AHRQ Comparative Effectiveness Review Surveillance Program

CER #31:
Effectiveness of Early Diagnosis, Prevention, and Treatment of *Clostridium difficile* Infection

Original release date:
December 2011

Surveillance Report (1st assessment/cycle 1):
October 2012

Surveillance Report (2nd assessment/cycle 2):
January 2014

Key Findings (1st assessment/cycle 1):

- One of three conclusions for Key Question 1, two of eight conclusions for Key Question 2, one of three conclusions for Key Question 3, and one of five conclusions for Key Question 4 are possibly out of date.
- There are no new significant safety concerns.

Key Findings (Cumulative: 1st and 2nd assessment/cycle 1-2):

- For Key Question 1, conclusions on comparative effectiveness of diagnostic agents are considered out of date due to increased evidence on PCR techniques for diagnosis.
- For Key Question 2, conclusions regarding prevention are possibly out of date.
- For Key Question 3, conclusions regarding treatment are possibly out of date.
- For Key Question 4, conclusions on nonstandard adjunctive therapies are considered out of date due to new information on fecal transplantation.

Summary Decision

This CER's priority for updating is **High** (changed from the first assessment)

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None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project:

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Effectiveness of Early Diagnosis, Prevention, and Treatment of *Clostridium difficile* Infection

1. Introduction

Comparative Effectiveness Review (CER) #31, Effectiveness of Early Diagnosis, Prevention, and Treatment of Clostridium difficile Infection[1], was released in December 2011. A previous surveillance assessment was performed in in June, 2012 and this topic was identified as due for another surveillance update in January 2014. As part of the surveillance assessment, we contacted experts involved in the original CER to gather their expert opinions on whether, based on their knowledge of the recent scientific literature, the conclusions of the 2012 surveillance report may need to be changed and whether the original 2011 CER needed to be updated again. We also conducted an independent electronic literature search update. Furthermore, we conducted searches of the US Food and Drug Administration (FDA), Health Canada, and UK Medicines and Healthcare Regulatory Agency (MHRA) databases for safety alerts on diagnostic tests, preventative interventions, treatment medications, and nonstandard adjunctive interventions. The diagnostic testing mechanisms, preventative interventions, treatment medications, and adjunctive therapies included in this surveillance assessment are listed below.

2. Methods

2.1 Literature Searches

Cycle 2 (2nd assessment)

In general, we used the same search strategy employed in the original 2011 CER. We did not use the search strategy specified by the first surveillance report conducted in 2012 because it focused exclusively on diagnostic testing. The search included five high-profile general medical interest journals (Annals of Internal Medicine, Journal of the American Medical Association, British Medical Journal, Lancet, and the New England Journal of Medicine), and five specialty journals (Clinical Infectious Diseases, Journal of Gastroenterology, Journal of Hospital Infection, Journal of Clinical Microbiology, and Infection Control and Hospital Epidemiology). Our search covered the time period of June 6 2010 through December 31, 2013; the original 2011 report searched through June 2010.

Cycle 1 (1st assessment)

Using the search strategy employed for the original report, we conducted a limited literature search of Medline for the years 2010 to June 5, 2012. The search included five high-profile general medical interest journals (Annals of Internal Medicine, British Medical Journal, Journal of the American Medical Association, Lancet, and the New England Journal of Medicine) and five specialty journals (Clinical Infectious Diseases, Journal of Gastroenterology, Journal of Hospital Infection, Journal of Clinical Microbiology, and Infection Control and Hospital Epidemiology). The specialty journals were those most highly represented among the references for the original report. Appendix A includes the search methodology for this topic.

2.2 Study Selection

Cycle 2 (2nd assessment)

In general, we used the same inclusion and exclusion criteria as the original 2011 CER. For Key Question 1, included studies needed to have used clinical stool specimen, compared at least two diagnostic tests, and used a reference test (or combination of tests) to verify the results. For Key Question 2, only studies that reported incidence of CDI or other measures of CDI as an outcome were included. Studies that reported on intermediate outcomes, such as spore counts, were excluded. The original report also included risk factor studies if the reviewers determined they were of good quality. For Key Question 3, included studies needed to have compared two active antimicrobial treatments; however placebo-controlled studies were acceptable for metronidazole and vancomycin. In this review, we also accepted placebo-controlled studies for the newer drug, fidaxomicin that was approved by the FDA in May of 2011. For Key Question 4, all studies that examined nonstandard adjunctive therapies were included.

Cycle 1 (1st assessment)

In general we used the same inclusion and exclusion criteria as the original CER.

2.3 Expert Opinion

Cycle 2 (2nd assessment)

We shared the conclusions of the original report with five experts in the field, including the original project leaders and two original technical expert panel members, for their assessment of the need to update the report and their recommendations of any relevant new studies. Three subject matter experts, including two of the original CER authors, responded. Appendix C shows the questionnaire matrix used.

Cycle 1 (1st assessment)

We shared the conclusions of the original report with 6 experts in the field (including the original project leader, suggested field experts, original technical expert panel (TEP) members, and peer reviewers) for their assessment of the need to update the report and their recommendations of any relevant new studies; three subject matter experts responded.

2.4 Check for qualitative and quantitative signals

After abstracting details and findings for each new included study into an evidence table, we assessed whether the new findings provided a "signal" according to the Ottawa Method and used the RAND Method to determine whether these signals suggested the need for an update. The criteria to define a "signal" or need for update are listed in the table below.[2, 3]

	Ottawa Method

	Ottawa Qualitative Criteria for Signals of Potentially Invalidating Changes in Evidence
A1	Opposing findings: A pivotal trial or systematic review (or guidelines) including at least one new trial that characterized the treatment in terms opposite to those used earlier.
A2	Substantial harm: A pivotal trial or systematic review (or guidelines) whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision making.
A3	A superior new treatment: A pivotal trial or systematic review (or guidelines) whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm.
	Criteria for Signals of Major Changes in Evidence
A4	Important changes in effectiveness short of "opposing findings"
A5	Clinically important expansion of treatment
A6	Clinically important caveat
A7	Opposing findings from discordant meta-analysis or nonpivotal trial
	Quantitative Criteria for Signals of Potentially Invalidating Changes in Evidence
B1	A change in statistical significance (from nonsignificant to significant)
B2	A change in relative effect size of at least 50 percent
	RAND Method Indications for the Need for an Update
1	Original conclusion is still valid and this portion of the original report does not need updating
2	Original conclusion is possibly out of date and this portion of the original report may need updating
3	Original conclusion is probably out of date and this portion of the original report may need updating
4	Original conclusion is out of date

2.5 Compilation of Findings and Conclusions

We constructed a summary table that included the key questions, original conclusions, findings of the new literature search, relevant findings from a search of Clinicaltrials.gov, expert assessments, and any FDA or MHRA reports that pertained to each key question. To assess the conclusions in terms of the evidence that they might need updating, we used the 4-category scheme described in the table above for the RAND Method.

In making the decision to classify a CER conclusion into one category or another, we used the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as probably still valid with or without a need to update based on new evidence.
- If we found some new evidence that might change the CER conclusion, and /or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out of date.
- If we found substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as probably out of date.
- If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a

limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

2.6 Determining Priority for Updating

We used the following two criteria in making our final conclusion for this CER:

- How much of the CER is possibly, probably, or certainly out of date?
- How out of date is that portion of the CER? For example, would the potential changes to the conclusions involve refinement of original estimates or do the potential changes mean some therapies are no longer favored or may not exist? Is the portion of the CER that is probably or certainly out of date an issue of safety (a drug withdrawn from the market, a black box warning) or the availability of a new drug within class (the latter being less of a signal to update than the former)?

3. Results

3.1 Search

Cycle 2 (2nd assessment)

The literature search identified 80 titles on the diagnosis, treatment, and prevention of *Clostridium difficile*. After title and abstract review, we further reviewed the full text of 49 journal articles on *C. difficile.* The remaining titles were rejected because they clearly did not meet inclusion criteria for any of the review questions

Of the 49 articles that underwent full text screening, 3 were rejected because they did not meet the inclusion criteria of the original report (e.g., duration less than three months, no active comparator, not addressing any of the key questions) or examined therapies not available in the US. We did not have resources to apply formal quality ratings to each study; we however used our best judgment focusing on variables such as method of randomization, allocation, blinding, and methods of adverse events ascertainment for cohort studies.

The 46 remaining articles were abstracted into an evidence table (Appendix B) for this assessment.[4-49]

Cycle 1 (1st assessment)

The literature search identified 128 titles. After title and abstract review, 105 titles were rejected because they were editorials or letters or did not include topics of interest or did not address the key question. The remaining 23 journal articles went on for further review. Four additional articles were reviewed at the suggestion of the experts.

Thus, through literature searches and expert recommendations, 27 articles went on to full text review. Of these, 20 articles were rejected because they were did not include a comparison of interest or did not meet the inclusion criteria. One article was the journal article of the original report. Thus, 7 articles were abstracted into an evidence table (Appendix C). [50-56]

The FDA MedWatch searches identified no notifications of relevance.

3.2 Expert Opinion

Cycle 2 (2nd assessment)

Three of the CER authors responded to the questionnaire matrix. Their responses are summarized in Table 1 below. In addition, two technical expert panel members provided overall comments on the CER. One of the experts simply stated that an update is needed, and referred us to a recent *C. difficile* guideline publication. This publication was not captured in our search strategy because we restricted our parameters to only include clinical trials, systematic reviews, and meta-analyses. In addition, one expert indicated that any update should wait until additional data is available in the future. Two experts felt that the CER was out of date due to new evidence, and one of the experts highlighted the need for updating the diagnostic portion of the CER. In summary, the experts felt that the while some of the conclusions on the comparative effectiveness of the strategies for the diagnosis, treatment, and prevention of *C. difficile* may still be valid, the CER needs to be updated to reflect the availability of new evidence.

Cycle 1 (1st assessment)

In general, expert opinion thought that the conclusions were either almost certainly supported by the evidence or did not know.

3.3 Identifying qualitative and quantitative signals

Cycle 2 (2nd assessment)

Table 1 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts' assessments, and the recommendations of the Scientific Resource Center (SRC) regarding the need for update.

Forty-six studies were abstracted. Twenty-five of these studies were comparative diagnostic trials, and one was a meta-analysis of comparative diagnostic trials. Five studies addressed prevention, two of which were RCTs, two of which were prospective cohorts, and one of which was a quasi-experimental study design. There were ten studies looking at treatment, five of which were RCTs, two of which were retrospective cohort studies, four of which were descriptive studies (two of these were descriptive studies), and one of which was a safety analysis. The final four studies looked at nonstandard adjunctive therapies, three of which were RCTs, and one of which was a case-control study. The majority of the studies looking at diagnostics focused on the use of PCR techniques, and the majority of the studies looking at treatment focused on the drug fidaxomicin.

Cycle 1 (1st assessment)

Table 1 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts' assessments, the recommendations of the 4 Southern California Evidence-based Practice Center (SCEPC) regarding the need for update, and qualitative signals.

4. Conclusion

Summary results and conclusions according to the information collated from different sources (updating signals from studies identified through the update search, safety surveillance alerts, and expert opinion) are provided in Table 1 (Summary Table). Based on the assessments, this CER is categorized in **High** priority group for updating.

Table 1. Summary Table

Conclusions from CER Executive Summary	SRC Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion, EPC Investigator, Other Experts	Conclusions from SRC	
				Cycle 1 assessment	Cycle 2 Assessment
Key Question 1: How do different methods for detection of toxigenic C. difficile to assist with the diagnosis of CDI compare in their sensitivity and specificity? (a) Do the differences in performance measures vary with sample characteristics?					
Immunoassays for toxins A and B **Level of Evidence:** Low to moderate •Ten studies directly compared at least 2 immunoassays for toxins A and B, providing 16 pairwise comparisons of 7 different immunoassays. Comparative data were not found for many currently used tests. •There were no statistical differences between the sensitivities of immunoassays that were compared; however, the estimates of the differences in sensitivity were not very precise and could not rule out substantial differences. •Substantial differences in false positives (specificity) were not found among the tests that were compared.	***Cycle 2 (January 2014)***			**Conclusion is still valid and this portion of the CER does not need updating.**	**Original conclusion is probably out of date and this portion of the original report may need updating.**
	Two studies were in favor of chromogenic agar for the detection of C. difficile after culture in the laboratory.[7,43] One study suggests that the use PCR-based CDI testing methods could improve clinical and infection outcome control outcomes, compared to the use of EIAs for toxins A and B.[14] Another study suggests that alternative testing strategies should be standard for identifying C. difficile infection in children, stating that approximately 1/3 of EIA tests used to evaluate pediatric inpatients for CDI were falsely positive.[39]	No new data	One expert stated that this needs updating in response to the new available literature. One expert broadly stated that the review was in need of an update. One expert stated that a review should wait until more evidence is available.		
	Cycle 1 (October 2012)				
	No new evidence	No new data	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert did not know.		
Gene detection tests versus immunoassays for toxins A and B **Level of Evidence: Low to moderate** **•Four studies compared at least one toxin gene detection test to at least one immunoassay for toxins A and B, providing a total of nine direct comparisons. Comparative data were not always available for the three currently available gene detection tests.** **•The gene detection tests could be substantially more sensitive than many immunoassays for toxins A and B, with no or relatively modest loss of specificity.**	***Cycle 2 (Second Assessment)***			**Original conclusion is probably out of date and this portion of the original report may need updating.**	**Original conclusion is probably out of date and this portion of the original report may need updating.**
	One study confirmed that toxin EIAs should no longer be the standard of care for detecting toxigenic C. difficile in the United States.[25] 20 different studies found that gene detection tests and PCR were much more reliable than enzyme immunoassays (EIAs) and the assays that detect toxins A and B.[4,6,8,10,13,15,17,18,20,21,24,26,29,34,38,42,44,45,49] A meta-analysis concluded that real-time PCR has high sensitivity and specificity to confirm CDI, and that the overall diagnostic accuracy is variable and depends on CDI prevalence.[12] One study recommended a particular assay followed by PCR for confirmation.[9]	Health Canada recalled the Xpert C. difficile assay in 2012 because some reagents in the kit were contaminated with microbes which could impact assay procedure and or performance. No new information (positive or negative) since that recall. No new data from either the FDA or MHRA	One expert stated that this needs updating in response to the new available literature.		
	Cycle 1 (October 2012)				

	One study[52] found that adding clinical symptoms (such as diarrhea severity) had minimal change on sensitivity but significantly lowered specificity. A meta-analysis of 19 studies5 found that PCR (all variants) has a high sensitivity and specificity to confirm CDI.	No new data	One expert agreed that this conclusion was almost certainly still supported by the evidence. One expert thought it was out of date. One expert did not know.		
Patient characteristics **Level of Evidence:** Insufficient Insufficient patient information was provided in reports of comparative data.	***Cycle 2 (January 2014)***			**Original conclusion is probably out of date and this portion of the original report may need updating.**	**Original conclusion is probably out of date and this portion of the original report may need updating.**
	One study suggests that detection of C. difficile toxin is associated with higher rates of intestinal inflammation than is detection of toxigenic genes.46		One expert broadly stated that the review does need updating and referred us to her recent guideline publication, which recommends stratifying patients by disease status. One expert broadly stated that a review should wait until more evidence is available. One expert did not comment.		
	Cycle 1 (October 2012)				
	No new evidence	No new data	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert did not know.		
Key Question 2. What are effective prevention strategies? (a) What is the effectiveness of current prevention strategies? (b) What are the harms associated with prevention strategies? 3 (c) How sustainable are prevention practices in health care (outpatient, hospital inpatient, extended care) and community settings?					
Antibiotic use **Level of Evidence: Low** **•Sixteen studies, including six bundled prevention practice studies, found appropriate prescribing practices are associated with decreased CDI incidence.** **•Harms were not reported.**	***Cycle 2 (January 2014)***			**Conclusion is still valid and this portion of the CER does not need updating.**	**Conclusion is still valid and this portion of the CER does not need updating.**
	One study suggests that reductions in duration of antibiotic exposure, in conjunction with formulary restriction, could result in a reduction of nosocomial CDI.[23] Another found that prolonged exposure to non-CDI-related antimicrobials was associated with adverse clinical outcomes.[35] Another study suggests that a 2-step testing algorithm for C. difficile using rapid PCR confirmatory testing leads to decreased unnecessary anti-CDI antimicrobial use.[24] Another study found that antimicrobials are often used unnecessarily in patients with current or a recent history of CDI.[47]	No new data	**2014:** One expert broadly stated that the review does need updating and referred us to a recent guideline publication that addresses prevention. One expert broadly stated that a review should wait until more evidence is available. One expert did not comment.		
	Cycle 1 (October 2012)				
	No new evidence	No new data	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert did not know.		
Gloves	***Cycle 2 (January 2014)***			**Original conclusion is**	**Original conclusion is**

Level of Evidence: Low **One controlled trial found use of gloves in hospital settings reduced CDI incidence.**	No new evidence	No new data	One expert broadly stated that the review does need updating and referred us to a recent guideline publication. One expert broadly stated that a review should wait until more evidence is available. One expert did not comment.	**probably out of date and this portion of the original report may need updating.**	**probably out of date and this portion of the original report may need updating.**
	Cycle 1 (October 2012)				
	One prospective before-after study[53] found no difference in CDI rates in a trial of universal gloving with emollient-impregnated gloves	No new data	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert did not know.		
Disposable thermometer **Level of Evidence: Low** **Three time series/before–after studies, two with controls, found use of disposable thermometers in hospital settings reduced CDI incidence.**	***Cycle 2 (January 2014)***			**Conclusion is still valid and this portion of the CER does not need updating.**	**Conclusion is still valid and this portion of the CER does not need updating.**
	No new evidence	No new data	**2014:** One expert broadly stated that the review does need updating and referred us to a recent guideline publication that addresses prevention. One expert broadly stated that a review should wait until more evidence is available. One expert did not comment.		
	Cycle 1 (October 2012)				
	No new evidence	No new data	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert did not know.		
Handwashing/alcohol gel **Level of Evidence: Low** **•No study examined whether handwashing reduced CDI incidence.** **•Two studies, one controlled trial and one before–after study, of use of alcohol gel to reduce MRSA transmission did not find significant differences in CDI incidence.**	***Cycle 2 (January 2014)***			**Conclusion is still valid and this portion of the CER does not need updating.**	**Conclusion is still valid and this portion of the CER does not need updating.**
	No new evidence	No new data	One expert broadly stated that the review does need updating and referred us to a recent guideline publication that addresses prevention. One expert broadly stated that a review should wait until more evidence is available. One expert did not comment.		
	Cycle 1 (October 2012)				
	No new evidence	No new data	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert did not know.		

Disinfection **Level of Evidence: Low** **Thirteen before–after studies of outbreaks or endemic hospital settings found intensive disinfection with a chemical compound that kills C. difficile spores reduced CDI incidence.**	***Cycle 2 (January 2014)***			**Original conclusion is probably out of date and this portion of the original report may need updating.**	**Conclusion is still valid and this portion of the CER does not need updating.**
	One study suggest that daily disinfections of high-touch surfaces in isolation rooms may address an important source of health-care worker hand contamination and provide a useful adjunctive measure to reduce transmission.[31] Another study suggests that both HPV and UVC decontamination reduce bacterial contamination in patient rooms.[30] One study found that there was no change in the incidence of C. difficile hospital acquired infections with chlorhexidine baths.[16]	No new data	**2**One expert broadly stated that the review does need updating and referred us to a recent guideline publication that addresses prevention. One expert broadly stated that a review should wait until more evidence is available. One expert did not comment.		
	Cycle 1 (October 2012)				
	One study[54] found no change in the incidence of C. difficile hospital acquired infection among general medical patients with chlorhexadine bathing.	No new data	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert did not know.		
Sustainability **Level of Evidence: Insufficient** **No evidence was available.**	***Cycle 2 (January 2014)***			**Conclusion is still valid and this portion of the CER does not need updating.**	**Conclusion is still valid and this portion of the CER does not need updating.**
	No new evidence	No new data	One expert broadly stated that the review does need updating and referred us to a recent guideline publication that addresses prevention. One expert broadly stated that a review should wait until more evidence is available. One expert did not comment.		
	Cycle 1 (October 2012)				
	No new evidence	No new data	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert did not know.		
Risk Factors **Level of Evidence: Low** **•Ten observational studies found evidence that antibiotic use, whether specific or general, increased risk of CDI.** **•Severe underlying disease, acid suppression, and age are indicated as risk factors. A number of other potential factors may be indicated in single studies.**	***Cycle 2 (January 2014)***			**Conclusion is still valid and this portion of the CER does not need updating.**	**Original conclusion is probably out of date and this portion of the original report may need updating to reflect new findings and expert opinion.**
	One study found that a prior room occupant with CDI is a significant risk factor for CDI acquisition, independent of established CDI risk factors.[22]	No new data	One expert broadly stated that the review does need updating and referred us to a recent guideline publication that addresses prevention. One expert broadly stated that a review should wait until more evidence is available. One expert did not comment.		

	Cycle 1 (October 2012)				
	No new evidence	No new data	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert did not know.		
Multiple component strategies Level of Evidence: Insufficient **•Eleven time series/before–after studies examined bundles of prevention components in a single intervention. Data are insufficient to draw conclusions.** **•Harms were not reported.**	***Cycle 2 (January 2014)***			**Conclusion is still valid and this portion of the CER does not need updating.**	**Conclusion is still valid and this portion of the CER does not need updating.**
	No new evidence	No new data	One expert broadly stated that the review does need updating and referred us to a recent guideline publication that addresses prevention. One expert broadly stated that a review should wait until more evidence is available. One expert did not comment.		
	Cycle 1 (October 2012)				
	No new evidence	No new data	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert did not know.		
Key Question 3: What are the comparative effectiveness and harms of different antibiotic treatments? (a) Does effectiveness vary by disease severity or strain? (b) Does effectiveness vary by patient characteristics: age, gender, comorbidity, hospital versus community-acquired setting? (c) How do prevention and treatment of CDI affect resistance of other pathogens?					
Vancomycin versus metronidazole Level of Evidence: Moderate for clinical cure, low for all other outcomes **•There were 3 head-to-head trials with a total of 335 subjects. Trials used various definitions of CDI patient and cure, especially with regard to stool count and consistency.** **•No significant differences in outcomes, including initial cure, clinical recurrence, and mean days to resolved diarrhea, were found.** **•Our results build upon, and are consistent with, the Cochrane Reviews search completed by Bricker et al.[1]**	***Cycle 2 (January 2014)***			**Conclusion is still valid and this portion of the CER does not need updating.**	**Original conclusion is probably out of date and this portion of the original report may need updating to reflect updated expert opinion.**
	No new evidence	No new data	One expert broadly stated that the review does need updating and referred us to a recent guideline publication that addresses treatments by disease stratification. This guideline stated that metronidazole remains the choice for mild-moderate disease but may not be sufficient for severe disease. One expert broadly stated that a review should wait until more evidence is available. One expert did not comment.		
	Cycle 1 (October 2012)				
	No new evidence	No new data	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert did not know.		
Severe disease, vancomycin versus	***Cycle 2 (January 2014)***			**Conclusion is still**	**Conclusion is still valid**

metronidazole **Level of Evidence: Insufficient** **One RCT examined a pre-specified subgroup of 69 subjects with severe CDI; improved clinical cure was based on per-protocol analysis, but not with strict intention-to-treat analysis.**	No new evidence	No new data	One expert broadly stated that the review does need updating and referred us to a recent guideline publication that addresses treatments by disease stratification. This guideline stated that metronidazole remains the choice for mild-moderate disease but may not be sufficient for severe disease. One expert broadly stated that a review should wait until more evidence is available. One expert did not comment.	**valid and this portion of the CER does not need updating.**	**and this portion of the CER does not need updating.**
	Cycle 1 (October 2012)				
	No new evidence	No new data	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert did not know.		
Fidaxomicin versus vancomycin **Level of Evidence: Moderate** **One large, high-quality RCT demonstrated decreased recurrence among those receiving fidaxomicin.**	***Cycle 2 (January 2014)***			**Original conclusion is probably out of date and this portion of the original report may need updating**	**Original conclusion is probably out of date and this portion of the original report may need updating.**
	Seven studies examined fidaxomicin and their results demonstrated increased efficacy, improved preservation of the intestinal microbiome, and that the drug appears to be well-tolerated. Most of these studies used vancomycin as a comparator.[19,27,28,32,33,37,40]	No new data	One expert broadly stated that the review does need updating and referred us to a recent guideline publication that addresses treatments by disease stratification. This guideline stated that metronidazole remains the choice for mild-moderate disease but may not be sufficient for severe disease. One expert broadly stated that a review should wait until more evidence is available. One expert did not comment.		
	Cycle 1 (October 2012)				
	One meta-analysis of two recently completed phase three trials[55] showed that fidaxomicin reduced persistent diarrhea, recurrence or death compared with vancomycin. A subgroup analysis[56] found that fidaxomicin was more effective than vancomycin in achieving clinical cure in the presence of concomitant antibiotics.	No new data	One expert agreed that this conclusion was almost certainly still supported by the evidence. Two experts did not know.		
All other comparisons of standard	***Cycle 2 (January 2014)***			**Conclusion is still**	**Original conclusion is**

treatments **Level of Evidence: Moderate for vancomycin versus fidaxomicin, low for all other comparisons There were eight trials examining: vancomycin versus bacitracin (two trials), vancomycin versus fidaxomicin, vancomycin versus nitazoxanide, vancomycin high versus low dose, vancomycin versus placebo, metronidazole versus nitazoxanide, and metronidazole versus metronidazole plus rifampin (one each). No differences.**	Seven studies examined fidaxomicin and their results demonstrated increased efficacy, improved preservation of the intestinal microbiome, and that the drug appears to be well-tolerated. Most of these studies used vancomycin as a comparator.[19,27,28,32,33,37,40]	No new data	One expert broadly stated that the review does need updating and referred us to a recent guideline publication that addresses treatments by disease stratification. This guideline stated that metronidazole remains the choice for mild-moderate disease but may not be sufficient for severe disease. One expert broadly stated that a review should wait until more evidence is available. One expert did not comment.	**valid and this portion of the CER does not need updating.**	**probably out of date and this portion of the original report may need updating.**
	Cycle 1 (October 2012)				
	No new evidence	No new data	One expert agreed that this conclusion was almost certainly still supported by the evidence. Two experts did not know.		
Strain of organism **Level of Evidence: Low** **One RCT (fidaxomicin vs. vancomycin) demonstrated decreased recurrence among those receiving fidaxomicin when the infecting organism was a non-NAP1 strain.**	***Cycle 2 (January 2014)***			**Conclusion is still valid and this portion of the CER does not need updating.**	**Conclusion is still valid and this portion of the CER does not need updating.**
	No new evidence	No new data	One expert broadly stated that the review does need updating and referred us to a recent guideline publication. One expert broadly stated that a review should wait until more evidence is available. One expert did not comment.		
	Cycle 1 (October 2012)				
	No new evidence	No new data	One expert agreed that this conclusion was almost certainly still supported by the evidence. Two experts did not know.		
Patient characteristics **Level of Evidence: Insufficient** **No comparative data were available.**	***Cycle 2 (January 2014)***			**Conclusion is still valid and this portion of the CER does not need updating.**	**Conclusion is still valid and this portion of the CER does not need updating.**
	No new evidence	No new data	One expert broadly stated that the review does need updating and referred us to a recent guideline publication that addresses treatments by disease stratification. One expert broadly stated that a review should wait until more evidence is available. One expert did not comment.		

	Cycle 1 (October 2012)				
	No new evidence	No new data	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert did not know.		
Resistance of other pathogens **Level of Evidence: Insufficient** **No data were available.**	***Cycle 2 (January 2014)***			**Conclusion is still valid and this portion of the CER does not need updating.**	**Original conclusion is probably out of date and this portion of the original report may need updating.**
	One study found that fidaxomicin did not suppress Bacteroides organisms and was less likely than vancomycin to promote acquisition of VRE or Candida species during CDI treatment.[33]	No new data	One expert broadly stated that the review does need updating and referred us to a recent guideline publication. One expert broadly stated that a review should wait until more evidence is available. One expert did not comment.		
	Cycle 1 (October 2012)				
	No new evidence	No new data	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert did not know.		
Key Question 4: What are the effectiveness and harms of nonstandard adjunctive interventions? (a) In patients with relapse/recurrent CDI?					
Treating CDI, active control **Level of Evidence: Low** **Probiotics, prebiotics, C. difficile immune whey, and colestipol are not more effective in treating CDI than standard antibiotic treatment with oral vancomycin or metronidazole or placebo.**	***Cycle 2 (January 2014)***			**Conclusion is still valid and this portion of the CER does not need updating.**	**Conclusion is still valid and this portion of the CER does not need updating.**
	No new evidence	No new data	One expert broadly stated that the review does need updating and referred us to a recent guideline publication. One expert broadly stated that a review should wait until more evidence is available. One expert did not comment.		
	Cycle 1 (October 2012)				
	No new evidence	No new data	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert cited new evidence of an additional harm.		
Treating CDI, placebo **Level of Evidence: Low** **Administration of a probiotic with live bacteria to treat CDI in critically ill patients increases risk for greater morbidity and mortality from fungemia without any known benefit.**	***Cycle 2 (January 2014)***			**Conclusion is still valid and this portion of the CER does not need updating.**	**Original conclusion is probably out of date and this portion of the original report may need updating.**
	One study found that the proprietary probiotic blend used was well-tolerated and effective for reducing risk of AAD and, in particular, CDAD in hospitalized patients on antibiotics. A dose-ranging effect was shown with 100	No new data	One expert broadly stated that the review does need updating and referred us to a recent guideline publication. One expert broadly stated that a review should wait until more evidence is		

	billion CFU, yielding superior outcomes and fewer gastrointestinal events compared to 50 billion CFU.[5]		available. One expert did not comment.		
	Cycle 1 (October 2012)				
	No new evidence	No new data	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert did not know.		
Treating recurrent CDI **Level of Evidence: Low** **There is limited evidence from two case series that fecal flora reconstitution is effective in treating recurrent CDI for up to 1 year.**	***Cycle 2 (January 2014)***			**Original conclusion is possibly out of date and this portion of the original report may need updating**	**Original conclusion is probably out of date and this portion of the original report may need updating.**
	One study found that infusion of donor feces was significantly more effective for the treatment of recurrent C. difficile infection than the use of vancomycin. In particular, patients with multiple relapses of C. difficile infection benefited from this unconventional approach.[48] In a separate search focusing exclusively on fecal microbiota transplantation (FMT) for the treatment of C. difficile, nine studies were identified as relevant, all of which were in favor of FMT. There were also 14 ongoing clinical trials identified on ClinicaTrials.gov investigating FMT in the treatment of C. difficile infections.[§]	No new data	One expert broadly stated that the review does need updating and referred us to a recent guideline publication. One expert broadly stated that a review should wait until more evidence is available. One expert did not comment.		
	Cycle 1 (October 2012)				
	No new evidence	One systematic review[50] found intestinal microbiota transplantation to be highly effective with disease resolution in 92% of cases.	Three experts agreed that this conclusion was almost certainly still supported by the evidence.		
Preventing CDI **Level of Evidence: Low** **There is limited evidence that the nonstandard interventions in this review are not more effective than placebo for primary prevention of CDI.**	***Cycle 2 (January 2014)***			**Conclusion is still valid and this portion of the CER does not need updating.**	**Original conclusion is probably out of date and this portion of the original report may need updating.**
	One study found no statistically significant differences were observed in relation to the other studied outcomes with single-dose intravenous immunoglobulin regimen.[11]	No new data	One expert broadly stated that the review does need updating and referred us to a recent guideline publication. One expert broadly stated that a review should wait until more evidence is		

			available. One expert did not comment.		
	Cycle 1 (October 2012)				
	No new evidence	No new data	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert did not know.		
Preventing recurrent CDI **Level of Evidence: Low to moderate** **•There is limited evidence from one subgroup analysis that a prebiotic may reduce diarrhea recurrence in patients treated for CDI more so than placebo with standard antibiotics.** **•There is limited moderate-strength evidence from one study that monoclonal antibodies are effective in preventing recurrence of CDI.**	***Cycle 2 (January 2014)***			Conclusion is still valid and this portion of the CER does not need updating.	Original conclusion is probably out of date and this portion of the original report may need updating.
	One study identified no evidence that a multistrain preparation of lactobacilli and bifidobacteria was effective in prevention of AAD or CDD.[41] Another study found that *S. boulardii* was unable to prevent the development of AAD, at least in a context with a low incidence of AAD cases.[36]	No new data	One expert broadly stated that the review does need updating and referred us to a recent guideline publication. One expert broadly stated that a review should wait until more evidence is available. One expert did not comment.		
	Cycle 1 (October 2012)				
	No new evidence	No new data	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert did not know.		

[§]Please refer to topic brief 0585 (Treatment for Clostridium difficile infection) for these references.

References

1. Butler M, Bliss D, Filice G, et al. Effectiveness of Early Diagnosis, Prevention, and Treatment of Clostridium difficile Infection. Comparative Effectiveness Review No. 31. Rockville, MD: Agency for Healthcare Research and Quality, December 2011.

2. Shekelle PG, Newberry SJ, Maglione M, et al. Assessment of the Need to Update Comparative Effectiveness Reviews: Report of an Initial Rapid Program Assessment (2005-2009). October 2009.

3. Shojania KG, Sampson M, Ansari MT, et al. How quickly do systematic reviews go out of date? A survival analysis. Ann Intern Med. 2007;147(4):224-33.17638714

4. Babady NE; Stiles J; Ruggiero P; et al. Evaluation of the Cepheid Xpert Clostridium difficile Epi assay for the diagnosis of Clostridium difficile infection and typing of the NAP1 strain at a cancer hospital. J Clin Microbiol. 2010;48(12):4519-4524.

5. Gao XW; Mubasher M; Fang CY; et al. Dose-response efficacy of a proprietary probiotic formula of Lactobacillus acidophilus CL1285 and Lactobacillus casei LBC80R for antibiotic-associated diarrhea and Clostridium difficile-associated diarrhea. Am J Gastroenterol. 2010;105:1636-1641.

6. Goldenberg SD; Cliff PR; French GL. Laboratory diagnosis of Clostridium difficile infection. J Clin Microbiol. 2010;48(8):3048-3049.

7. Perry JD; Asir K; Malimi D; et al. Evaluation of a chromogenic culture medium for isolation of Clostridium difficile within 24 hours. J Clin Microbiol. 2010;48(11)3852-3858.

8. Ryder AB; Huang Y; Li H; et al. Assessment of Clostridium difficile infections by quantitative detection of tcdB toxin by use of a real-time cell analysis system. J Clin Microbiol. 2010;48(11):4129-4134.

9. Sharp SE; Ruden LO; Pohl JC; et al. Evaluation of the C.Diff Quik Chek Complete assay, a new glutamate dehydrogenase and A/B toxin combination lateral flow assay for use in rapid, simple diagnosis of Clostridium difficile disease. J Clin Microbiol. 2010;48(6):2082-2086.

10. Tenover FC; Novak-Weekley S; Woods CW; et al. Impact of strain type on detection of toxigenic Clostridium difficile: comparison of molecular diagnostic and enzyme immunoassay approaches. J Clin Microbiol. 2010;48(10):3719-3724.

11. Aldeyab MA; McEnlay JC; Scott MG; et al. An evaluation of the impact of a single-dose intravenous immunoglobulin regimen in the treatment of Clostridium difficile infection. Infect Control Hosp Epidemiol. 2011;32(6):631-633.

12. Deshpande A; Paupuleti V; Rolston DDK; et al. Diagnostic accuracy of real-time polymerase chain reaction in detection of Clostridium difficile in the stool samples of patients with suspected Clostridium difficile infection: a meta-analysis. Clin Infect Dis. 2011;53(7):e81-e90.

13. Eckert C; Van Broeck J; Spigaglia P; et al. Comparison of a commercially available repetitive-element PCR system (DiversiLab) with PCR ribotyping for typing of Clostridium difficile strains. J Clin Microbiol. 2011;49(9):3352-3354.

14. Guerrero DM; Chou C; Jury LA; et al. Clinical and infection control implications of Clostridium difficile infection with negative enzyme immunoassay for toxin. Clin Infect Dis. 2011;53(3):278-290.

15. Karre T; Sloan L; Patel R; et al. Comparison of two commercial molecular assays to a laboratory-developed molecular assay for diagnosis of Clostridium difficile infection. J Clin Microbiol. 2011;49(2):725-727.

16. Kassakian SZ; Mermel LA; Jefferson JA; et al. Impact of Chlorhexidine bathing on hospital-acquired infections among general medical patients. Infect Control Hosp Epidemiol. 2011;33(3):238-243.

17. Knetsch CW; Bakker D; de Boer RF; et al. Comparison of real-time PCR techniques to cytotoxigenic culture methods diagnosing Clostridium difficile infection. J Clin Microbiol. 2011;49(1):227-231.

18. Lalande V; Barrault L Wadel S; et al. Evaluation of a loop-mediated isothermal amplification assay for diagnosis of Clostridium difficile infections. J Clin Microbiol. 2011;49(7):2714-2716.

19. Louie TJ; Miller MA; Mullane KM; et al. Fidaxomicin versus vancomycin for Clostridium difficile infection. N Engl J Med. 2011;364:422-431.

20. Luna RA; Boyanton BL; Mehta S; et al. Rapid stool-based diagnosis of Clostridium difficile infection by real-time PCR in a children's hospital. J Clin Microbiol. 2011;49(3):853-857.

21. Noren T; Alriksson I; Andersson J; et al. Rapid and sensitive loop-mediated isothermal amplification test for Clostridium difficile detection challenges cytotoxin B cell test and culture as gold standard. J Clin Microbiol. 2011;49(2):710-711.

22. Shaughnessy MK; Micielli RL; DePestel DD; et al. Evaluation of hospital room assignment and acquisition of Clostridium difficile infection. Infect Control Hosp Epidemiol. 2011;33(11):201-206.

23. Stevens V; Dumyati G; Fine LS; et al. Cumulative antibiotic exposures over time and the risk of Clostridium difficile infection. Clin Infect Dis. 2011;53(1):42-48.

24. Sydnor ERM; Lenhart A; Trollinger B; et al. Antimicrobial prescribing practices in response to different Clostridium difficile diagnostic methodologies. Infect Control Hosp Epidemiol. 2011;32(11):1133-1136.

25. Boyanton BL; Sural P; Loomis CR; et al. Loop-mediated isothermal amplification compared to real-time PCR and enzyme immunoassay for toxigenic Clostridium difficile detection. J Clin Microbiol. 2012;50(3):640-645.

26. Buchan BW; Mackey TA; Daly JA; et al. Multicenter clinical evaluation of the Portrait Toxigenic C. difficile assay for the detection of toxigenic Clostridium

difficile strains in clinical stool specimens. J Clin Microbiol. 2012;50(12);3932-3936.

27. Cornely OA; Miller MA; Louie TJ; et al. Treatment of first recurrence of Clostridium difficile infection: fidaxomicin versus vancomycin. Clin Infect Dis. 2012;55(S2):S154-S161.

28. Figueroa R; Johnson S; Sambol S; et al. Relapse versus reinfection: recurrent Clostridium difficile infection following treatment with fidaxomicin or vancomycin. Clin Infect Dis. 2012;S55(S2):S104-S109.

29. Hardy K; Manzoor S; Marriot C; et al. Utilizing rapid multiple-locus variable-number tandem-repeat analysis typing to aid control of hospital-acquired Clostridium difficile infection: a multicenter study. J Clin Microbiol. 2012;50(10): 3244-3248

30. Havill NL; Moore BA; Boyce JM. Comparison of the microbiological efficacy of hydrogen peroxide vapor and ultraviolet light processes for room decontamination. Infect Control Hosp Epidemiol. 2012;33(5):507-512.

31. Kundrapu S; Sunkesula V; Jury LA; et al. Daily disinfection of high-touch surfaces in isolation rooms to reduce contamination of healthcare workers' hands. Infect Control Hosp Epidemiol. 2012;33(10):1039-1042.

32. Louie TJ; Cannon K; Byrne B; et al. Fidaxomicin preserves the intestinal microbiome during and after treatment of Clostridium difficile infection (CDI) and reduces both toxin reexpression and recurrence of CDI. Clin Infect Dis. 2012;55(S2):S132-S142.

33. Nerandzic MM; Mullane K; Miller MA; et al. Reduced acquisition and overgrowth of vancomycin-resistant enterococci and Candida species in patients treated with fidaxomicin versus vancomycin for Clostridium difficile infection. Clin Infect Dis. 2012;55(S2):S121-S126.

34. Pancholi P; Kelly C; Raczkowski M; Balada-Llasat JM. Detection of toxigenic Clostridium difficile: comparison of the cell culture neutralization, Xpert C. difficile, Xpert C. difficile/Epi, and Illumigene C. difficile assays. J Clin Microbiol. 2012;50(4):1331-1335.

35. Pop-Vicas A; Shaban E; Letourneau C; Pechie A. Empirical antimicrobial prescriptions in patients with Clostridium difficile infection at hospital admission and impact on clinical outcome. Infect Control Hosp Epidemiol. 2012;33(11):1101-1106.

36. Pozzoni P; Riva A; Bellatorre AG; et al. Saccharomyces boulardii for the prevention of antibiotic-associated diarrhea in adult hospitalized patients: a single-center, randomized, double-blind, placebo-controlled trial. Am J Gastroenterol. 2012;107:922-931.

37. Sears P; Crook DW; Louie TJ; et al. Fidaxomicin attains high fecal concentrations with minimal plasma concentrations following oral administration in patients with Clostridium difficile infection. Clin Infect Dis. 2012;55(S2);S116-S120.

38. Shin B; Mun SJ; Yoo SJ; Kuak EY. Comparison of the BD GeneOhm Cdiff and Seegene Seeplex ACE PCR assays

using toxigenic Clostridium difficile culture for direct detection of tcdB from stool specimens. J Clin Microbiol. 2012;50(11)3765-3767.

39. Toltzis P; Nerandzic MM; Saade E; et al. High proportion of false-positive Clostridium difficile enzyme immunoassays for toxin A and B in pediatric patients. Infect Control Hosp Epidemiol. 2012;33(2):175-179.

40. Weiss K; Allgren RL; Sellers S. Safety analysis of fidaxomicin in comparison with oral vancomycin for Clostridium difficile infections. Clin Infect Dis. 2012;55(S2):S110-S115.

41. Allen SJ; Wareham K; Wang D; et al. Lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhoea and Clostridium difficile diarrhoea in older inpatients (PLACIDE): a randomized, double-blind, placebo-controlled, multicenter trial. Lancet. 2013; 382: 1249-1257.

42. Dalpke AH; Hofko M; Zorn M; Zimmermann S. Evaluation of the fully automated BD MAX Cdiff and Xpert C. difficile assays for direct detection of Clostridium difficile in stool specimens. J Clin Microbiol. 2013;51(5):1906-1908

43. Eckert C; Burghoffer B; Lalande V; Barbut F. Evaluation of the chromogenic agar chromID C. difficile. J Clin Microbiol. 2013;51(3):1002-1004.

44. Gyorke CE; Wang S; Leslie JL; et al. Evaluation of Clostridium difficile fecal load and limit of detection during a prospective comparison of two molecular tests, the Illumigene C. difficile and Xpert C. difficile/Epi tests. J Clin Microbiol. 2013 (51(1):278-280.

45. Humphries RM; Uslan DZ; Rubin Z. Performance of Clostridium difficile toxin enzyme immunoassay and nucleic acid amplification tests stratified by patient and disease severity. J Clin Microbiol. 2013;51(3):869-873.

46. LaSala PR; Ekhmimi T; Hill AK; et al. Quantitative fecal lactoferrin in toxin-positive and toxin-negative Clostridium difficile specimens. J Clin Microbiol. 2013;51(1)311-313.

47. Shaughnessy MK; Amundson WH; Kuskowski MA; et al. Unnecessary antimicrobial use in patients with current or recurrent Clostridium difficile infection. Infect Control Hosp Epidemiol. 2013;34(2)109-116.

48. Van Nood E; Vrieze A; Nieuwdorp M; et al. Duodenal infusion of donor feces for recurrent Clostridium difficile. N Engl J Med. 2013;368:407-415.

49. Walkty A; Lagace-Wiens PRS; Manickam K; et al. Evaluation of an algorithmic approach in comparison with the Illumigene assay for laboratory diagnosis of Clostridium difficile infection. J Clin Microbiol. 2013;51(4)1152-1157.

50. Gough E, Shaikh H, Manges AR. Systematic review of intestinal microbiota transplantation (fecal 12 bacteriotherapy) for recurrent Clostridium difficile infection. Clin Infect Dis. 2011;53(10):994-1002.

51. Dubberke ER, Han Z, Bobo L, et al. Impact of clinical symptoms on interpretation of diagnostic assays for Clostridium difficile infections. *Journal*

of Clinical Microbiology. 2011;49(8):2887-93.21697328

52. Deshpande A, Pasupuleti V, Rolston DDK, et al. Diagnostic accuracy of real-time polymerase chain reaction in detection of Clostridium difficile in the stool samples of patients with suspected Clostridium difficile Infection: a meta-analysis. *Clin Infect Dis*. 2011;53(7):e81-90.21890762

53. Bearman G, Rosato AE, Duane TM, et al. Trial of universal gloving with emollient-impregnated gloves to promote skin health and prevent the transmission of multidrug-resistant organisms in a surgical intensive care unit. *Infect Control Hosp Epidemiol*. 2010;31(5):491-7.20350197

54. Kassakian SZ, Mermel LA, Jefferson JA, et al. Impact of chlorhexidine bathing on hospital-acquired infections among general medical patients. *Infect Control Hosp Epidemiol*. 2011;32(3):238-43.21460508

55. Crook DW, Walker AS, Kean Y, et al. Fidaxomicin versus vancomycin for Clostridium difficile infection: meta-analysis of pivotal randomized controlled trials. *Clin Infect Dis*. 2012;55 Suppl 2:S93-103.22752871

56. Mullane KM, Miller MA, Weiss K, et al. Efficacy of fidaxomicin versus vancomycin as therapy for Clostridium difficile infection in individuals taking concomitant antibiotics for other concurrent infections.[Erratum appears in Clin Infect Dis. 2011 Dec;53(12):1312 Note: Dosage error in article text]. *Clin Infect Dis*. 2011;53(5):440-7.21844027

Appendix A. Search Methodology

Cycle 2 (Second Assessment)

DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 06/01/2010-12/31/2013

LANGUAGE:
English

SEARCH STRATEGY:

((("Clostridium difficile"[majr] OR "Clostridium difficile"[tiab] OR "C. difficile"[tiab] AND (("2010/06/01"[PDat] : "2013/12/31"[PDat])))) AND ("Ann Intern Med"[Journal] OR BMJ[Journal] OR JAMA[Journal] OR Lancet[Journal] OR "N Engl J Med"[Journal] OR "Am J Gastroenterol"[Journal] OR "Clin infect dis"[Journal] OR "infect control hosp epidemiol"[Journal] OR "J clin microbiol"[Journal] AND (("2010/06/01"[PDat] : "2013/12/31"[PDat]))) AND (("2010/06/01"[PDat] : "2013/12/31"[PDat]))

NUMBER OF RESULTS: 80

Cycle 1 (First Assessment)

SEARCH #1:
DATABASE SEARCHED & TIME PERIOD COVERED:
Medline on OVID – 2010-6/5/2012

LANGUAGE:
English

SEARCH STRATEGY:
difficile.mp.
AND
randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab. OR Cohort studies/ or comparative study/ or follow-up studies/ or prospective studies/ or risk factors/ or cohort.mp. or compared.mp. or groups.mp. or multivariate.mp.
NOT
addresses or bibliography or biography or dictionary or directory or duplicate publication or editorial or interview or introductory journal article or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or portraits OR comment or historical article
NOT
(animals not (humans and animals)).sh.

NUMBER OF RESULTS AFTER REMOVAL OF DUPLICATES: 595
==========

SEARCH #2 (DIAGNOSTIC ACCURACY)
DATABASE SEARCHED & TIME PERIOD COVERED:

Medline on OVID – 2010-6/6/2012

LANGUAGE:
English

SEARCH STRATEGY:
difficile.mp.
AND
diagnostic accuracy.mp. OR (enzyme adj2 immunoassay$).mp OR Immunoenzyme techniques/ OR enzyme linked immunosorbent assay/ OR feces/ OR faeces analysis.mp. OR fecal.mp. OR stool culture.mp. OR exp "Sensitivity and Specificity" OR cytotoxicity test, immunologic/ OR cell cytotoxicity assay.mp. OR pcr.mp. or polymerase chain reaction/ OR immunochromatography.mp.
NOT
(animals not (humans and animals)).sh.
NOT
addresses or bibliography or biography or dictionary or directory or duplicate publication or editorial or interactive tutorial or interview or introductory journal article or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or portraits
NOT in vitro

NUMBER OF RESULTS: 417

RESULTS LIMITED TO THE FOLLOWING JOURNALS:
Annals of Internal Medicine
BMJ
JAMA
Lancet
New England Journal of Medicine
Clinical Infectious Disease Gastroenterology Journal of Hospital Infection Journal of ClinicalMicrobiology Infection Control and Hospital Epidemiology

NUMBER OF RESULTS AFTER FILTERING FOR SPECIFIED JOURNALS: 128

Appendix B: Evidence Table (Cycle 2/2nd Assessment)

Author	Year	Title	Participants	Intervention groups	Treatment duration	Primary outcome	Findings
Key Question 1: How do different methods for detection of toxigenic C. difficile to assist with the diagnosis of CDI compare in their sensitivity and specificity? (a) Do the differences in performance measures vary with sample characteristics?							
Babady et al[4]	2010	Evaluation of Cepheid Xpert Clostridium difficile Epi Assay for diagnosis of Clostridium difficile infection and typing of the NAP1 strain at a cancer hospital	Phase 1: 44 positive stool samples from 39 patients Phase 2: 60 positive stool samples from 47 patients	glutamate dehydrogenase (GDH) followed by cytotoxin neutralization test (CYT) vs. Cepheid Xpert C. difficile Epi assay, with toxigenic culture to resolve discordant results.	N/A	sensitivity and specificity of the diagnostic tests	GDH-CYT and Xpert PCR had excellent specificity but marked differences in their sensitivity. The study determined that their GDH-CYT algorithm had a sensitivity of up to 61%, consistent with what has been reported in the literature. The authors concluded that in addition to an increase in analytical sensitivity, the greatest impact of adopting the Xpert PCR assay will be its value in effectively reducing the time patients are kept in isolation.
Boyanton et al.[25]	2012	Loop-mediated isothermal amplification compared to real-time PCR and enzyme immunoassay for toxigenic Clostridium difficile detection	fecal specimens from 139 hospitalized patients	Two molecular assays: Meridian illumigene and BD GeneOhm Two antigen assays: Wampole Quik Chek Complete and TechLab Tox A/B II	N/A	Incorporating clinical information and the results of toxigenic culture; sensitivity and specificity	Per the authors, the illumigene assay performed exceptionally well, with sensitivity and a specificity of 95.2% and 96.6%, respectively. The GeneOhm assay also performed exceptionally well, with sensitivity of 95.2% and specificity of 100%, minimally exceeding the performance of the illumigene assay. The Tox A/B II assay demonstrated poor sensitivity (52.4%). The high specificity of the Tox A/B II assay of 97.5% is congruent with the work of others. The Quik Chek performed similarly to the Tox A/B II. In summary, these results support the use of illumigene C. difficile assay.
Buchan et al[26]	2012	Multicenter clinical evaluation of the Portrait Toxigenic C. difficile assay for detection of Clostridium difficile strains in clinical stool specimens	549 fresh stool specimens from patients suspected of having C. difficile infection	Portrait assay; Xpert assay; Illumigene assay; and GeneOhm assay	N/A	sensitivity and specificity of the diagnostic tests	The sensitivities and specificities of the molecular tests from this study compared to TBC/CCNA were as follows: 98.2% and 92.8% for the Portrait assay, 100% and 91.7% for the Xpert assay, 93.3% and 95.1% for the Illumigene assay, and 97.4% and 98.5% for the GeneOhm assay, respectively. The majority of Portrait false-positive results (20/31, 64.5%) were also positive for C. difficile by an alternative molecular test. The sensitivity of the Portrait test was higher than those of 2 of 3 of the other evaluated molecular tests. Only the Xpert assay had a higher sensitivity (100%); however the specificity of the Portrait test was higher than that of the Xpert.
Dalpke et al.[42]	2013	Evaluation of the fully automated BD MAX Cdiff and Xpert C. difficile assays for direct detection of Clostridium difficile in stool specimens	448 stool specimens, mostly (94.9%) soft or liquid, were examined from 333 patients	BD MAX Cdiff assay; Xpert C. difficile assay	N/A	sensitivity and specificity of the diagnostic tests	Sensitivities, specificities, positive predictive values (PPV), and negative predictive values (NPV) from this study were 90.5%, 97.9%, 89.3%, and 98.1%, respectively, for BD MAX and 97.3%, 97.9%, 90.0%, and 99.5%, respectively, for Xpert. According to the authors, the results indicate that nucleic acid detection of C. difficile directly from stool specimens could serve as a rapid and reliable substitute for time-consuming culture.

Deshpande et al.[12]	2011	Diagnostic accuracy of real-time polymerase chain reaction in detection of Clostridium difficile in the stool samples of patients with suspected Clostridium difficile infection: a meta-analysis.	19 studies (7392 samples)	PCR detection of C. difficile infections	N/A	sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio, and the area under the curve.	In this study, the overall mean sensitivity of PCR was 90% (95% CI: 88-91%), specificity 96% (95% CI: 96-97%), positive likelihood ratio 26.89 (95% CI: 20.81-34.74), negative likelihood ratio 0.11 (95% CI: 0.08-0.15), diagnostic odds ratio 278.23 (95% CIL 213.56-362.50) and the area under the curve 0.98 (95% CI: 0.98-0.99). Per the authors, the test accuracy depended on the prevalence of C. difficile but not on the reference test used. At C. difficile prevalence of <10%, 10-20%, and >20% the positive predictive value and the negative predictive value were 71%, 79%, 93%, and 99%, 98%, and 96%, respectively. The study concluded that real-time PCR has a high sensitivity and specificity to confirm CDI. Overall, diagnostic accuracy is variable and depends on CDI prevalence.
Eckert et al.[13]	2011	Comparison of commercially available repetitive-element PCR system (DiversiLab) with PCR ribotyping for typing of Clostridium difficile strains.	69 strains of well-defined PCR ribotypes were studied	repetitive-element PCR method (DiversiLab system) to PCR ribotyping	N/A	discriminatory power in typing C. difficile	The authors of this study concluded that, compared to both manual rep-PCR and PCR ribotyping, the rep-PCR method (DiversiLab) showed a higher discriminatory power in typing C. difficile. This high discriminatory power may be helpful for investigating outbreaks and strain transmission from patient to patient, more particularly when a clone is predominant within a hospital, such as 027. The authors also cautioned that interlaboratory reproducibility should be assessed before using this technique for national or international surveillance of C. difficile genotypes.
Eckert et al.[43]	2013	Evaluation of the chromogenic agar chromID C. difficile	406 stool samples of patients suspected of having Clostridium difficile infection	three selective media: chromID C. difficile agar, taurocholate cycloserine cefoxitin agar (TCCA) CLO medium	N/A	sensitivities of chromID at 24h and 48h, and TCCA and CLO medium	This study examined the sensitivities of chromID C. difficile agar at 24h and 48h, CLO medium, and TCCA. The results were 74.1%, 87%, 85.2%, and 70.4%, respectively. Per the authors, for the in vitro comparison of sensitivity, there was a significant difference in recovery of C. difficile across the media (P<0.05). The mean concentrations (+/- standard deviations) of C. difficile on chromID C. difficile agar plates after 24h of incubation, chromID C. difficile agar plates after 48h incubation, CLO plates, and TCCA plates were 5.84 +/- 1.58, 6.27 +/- 1.3, 5.45 +/- 1.55, and 5.96 +/- 1.25 CFU/ml, respectively. When the media were compared pairwise, only CLO medium was significantly less sensitive than the chromID C. difficile agar at 48h (Tukey's multiple comparison test, <0.05).
Goldenberg et al.[6]	2010	Laboratory diagnosis of Clostridium difficile infection	not stated, assumed stool samples suspicious of C. difficile infection	C Diff Quik Chek 60 as screening test, followed by confirmation with GeneOhm PCR, compared to toxigenic culture for reference	N/A	sensitivity (95% CI); specificity (95% CI)	This study used C Diff Quik Chek 60 for GDH as a screening test, followed by confirmation with BD GeneOhm PCR for C. difficile. This experiment gave a sensitivity of 94% (95% CI: 80-99%), a specificity of 99% (95% CI: 98-99%), and an AU ROC of 0.97 (95% CI: 0.93 to 1.00) compared with toxigenic culture as a reference. The authors found that this was also statistically significantly better than an EIA alone, (Meridian Premier A/B EIA), which had a sensitivity of 39% (95% CI: 24-57%), a specificity of 99% (95% CI: 98-99%) and an AU ROC of 0.69 (95% CI: 0.61 to 0.77).

Guerrero et al.[14]	2011	Clinical and infection control implications of Clostridium difficile infection with negative enzyme immunoassay for toxin	132 patients who received a diagnosis of CDI based on the presence of unformed stool and positive glutamate dehydrogenase and PCR results	PCR results compared to enzyme immunoassay (EIA) results	N/A	efficacy of EIAs	The authors of this study found that nearly 1/3 of patients with CDI diagnosed using a two-step glutamate dehydrogenase and PCR testing algorithm would have been missed if only EIA for toxin testing had been performed. EIA-negative patients did not differ in clinical presentation from EIA-positive patients. Notably, 21% of EIA-negative patients presented with severe CDI, including one patient who died of fulminant CDI. Patients with negative EIA toxin results were also as likely as EIA-positive patients to shed spores onto their skin and into the environment. The authors suggest that these findings suggest that the use of PCR-based CDI testing methods could potentially improve clinical and infection control outcomes, compared with the use of EIA for toxins A and B.
Gyorke et al.[44]	2013	Evaluation of Clostridium difficile fecal load and limit of detection during a prospective comparison of two molecular tests, the illumigene C. difficile and Xpert C. difficile/Epi Tests	568 samples and patients were included in this analysis	fecal C. difficile DNA load of positive samples as part of a large, prospective comparison of two nucleic acid amplification tests (NAATs) for C. difficile, the illumigene C. difficile test and the Xpert C. difficile/Epi test, with toxigenic culture	N/A	Sensitivity	Overall, the authors found a 16% sensitivity difference between the illumigene C. difficile LAMP assay and the Xpert C. difficile/Epi real-time PCR test in a large-scale, prospective comparison with toxigenic culture. When the fecal toxin status of samples was considered, the illumigene and Xpert tests performed similarly and were both highly sensitive for toxin-positive samples, but the illumigene was much less sensitive with toxin-negative samples (58% for illumigene vs. 100% for Xpert; P<0.001). The authors concluded that these findings demonstrate a clinical sensitivity difference between the illumigene C. difficile assay and the Xpert C. difficile/Epi test at low C. difficile concentrations.
Hardy et al.[29]	2012	Utilizing rapid multi-locus variable-number tandem-repeat analysis typing to aid control of hospital-acquired Clostridium difficile infection: a multicenter study	1682 toxin-positive cases; 868 in the control arm and 814 in the test arm. A total of 245 PIIs occurred, involving 785 patients.	multiple-locus variable-number tandem-repeat analysis (MLVA) compared to typing using PCR ribotyping	N/A	mean turn-around time, discriminatory ability, responder opinion	In this study, there was a significant difference in mean turnaround time between ribotyping and MLVA typing (13.6 and 5.3 days, respectively [P<0.001]). The discriminatory ability of the MLVA was greater than ribotyping, with 85 outbreaks being confirmed by ribotyping and 62 by MLVA. In the test arm, 40.6% of respondents strongly agreed that the typing results aided their management of clusters, as opposed to 9.9% in the control. Per the authors, this study demonstrated the utility of rapidly typing C. difficile strains and that it aided the management of clusters, enabling effective targeting of infection control resources.
Humphries et al.[45]	2013	Performance of Clostridium difficile toxin enzyme immunoassay and nucleic acid amplification tests stratified by patient disease severity	296 hospital inpatients with diarrhea and clinical suspicion for CDI; 143 patients with CDI confirmed by toxigenic culture were evaluated in this study	Toxin EIA; C. difficile NAAT; confirmed by toxigenic culture	N/A	Sensitivity	For this study, among patients with mild CDI, 49% tested positive by toxin EIA and 98% tested positive by NAAT. Among patients with severe CDI, 58% tested positive by toxin EIA and 98% tested positive by NAAT. Increased CDI disease severity was not associated with increased sensitivity in toxin EIA (P=0.31). The authors concluded that the data demonstrate that toxin EIA performs poorly for patients with severe CDI and patients with mild CDI and support the use of NAAT for the diagnosis of CDI. The authors further concluded that even though NAATs are roughly ten times more expensive than EIAs on a per test basis, prompt recognition of CDI patients is imperative.

Karre et al.[15]	2011	Comparison of two commercial molecular assays to a laboratory-developed molecular assay for diagnosis of Clostridium difficile infection	346 soft or liquid stool specimens submitted to the Clinical Microbiology Laboratory, Mayo Clinic, from different patients for C. difficile testing by PCR assay (LC-CDTX assay) were used to compare three molecular assays.	Two commercial assays: Prodesse ProGastro CD assay BD GeneOhm Cdiff assay Laboratory-developed assay: LC-CDTX	N/A	sensitivities and specificities of the three assays	The authors of this study used positive results by all three molecular assays and/or a positive toxigenic culture result as the "gold standard," and determined that the sensitivities and specificities, respectively, of the three assays were 94.6% and 99.7% for the LC-CDTX assay (P=0.56), 83.8% and 99.4% for the BD GeneOhm Cdiff assay (P=0.16), and 91.9% and 99.0% for the ProGastro CD assay (P=1.0). They concluded that the results of the three methods were in agreement for 333 (96%) of 346 stool specimens. No significant difference in performance among the assays was found (P values >0.05).
Knetsch et al.[17]	2011	Comparison of Real-Time PCR techniques to cytotoxigenic culture methods for diagnosing Clostridium difficile infection	526 diarrheal samples were prospectively collected and included in the study	Two real-time PCRs (LUMC and LvI) targeting C. difficile toxin genes were compared with BD GeneOhm PCR, using cytotoxigenic culture as the gold standard. In addition, real-time PCR targeting the tcdC frameshift mutation at position 117 was evaluated for detecting toxigenic C. difficile and the presence of the PCR ribotype 027 in stool samples.	N/A	sensitivity, specificity, positive predictive value, negative predictive value.	Compared for those with cytotoxigenic culture, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were for the PCR LUMC 96.0%, 88.0%, 66.0%, and 98.9%, for PCR LvI 100%, 89.4%, 69.7%, and 100%, for PCRΔ117 98.0%, 90.7%, 71.9% and 99.5%, and for PCR BD GeneOhm 88.3%, 96.9%, 86.5%, and 97.4%. Compared to those with feces samples cultured positive for C. difficile type 027, the sensitivity, specificity, PPV, and NPV of the Δ117 PCR were 95.2%. 96.2%, 87%, and 98.7%. Given this data, the authors concluded that all real-time PCRs can be applied as a first screening test in an algorithm for diagnosing CDI.
Lalande et al.[18]	2011	Evaluation of a loop-mediated isothermal amplification assay for diagnosis of Clostridium difficile infections	472 unformed stools from patients suspected of Clostridium difficile infection	Illumigene assay; cytotoxic assay; toxigenic culture	N/A	sensitivity, specificity, positive predictive value, negative predictive value.	In this study, compared to the TC, the sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively) were 69.4, 100, 100, and 96.8% for CTA and 91.8, 99.1, 91.8, and 99.1% for the illumigene assay. The authors concluded the illumigene C. difficile assay is the first FDA-approved isothermal nucleic acid amplification-based assay. It offers sensitivity and specificity for the detection of toxigenic C. difficile strains that are comparable to those of the toxigenic culture reference method and other PCR-based methods.
LaSala et al.[46]	2013	Quantitative fecal lactoferrin in toxin-positive and toxin-negative Clostridium difficile specimens	112 patients tested for toxigenic C. difficile using glutamate dehydrogenase and toxin immunoassays combined with tcdB PCR	toxin positive; NAAT-positive/ toxin-negative; and NAAT-negative/toxin-negative patients	N/A	quantitative fecal lactoferrin	This study found that lactoferrin levels were higher in the GDH-positive/toxin-positive group than in the GDH-positive/toxin-negative/PCR-positive and the GDH negative groups. Differences in fecal lactoferrin levels suggest variable presence or severity of C. difficile infection among toxin-positive and toxin-negative patients. They concluded that the study suggests detection of C. difficile toxin is associated with higher rates of intestinal inflammation than is detection of toxigenic genes.

Luna et al.[20]	2011	Rapid stool-based diagnosis of Clostridium difficile infection by real-time PCR in a children's hospital	157 samples from 96 pediatric patients were analyzed	Culture: tcdA, tcdB, and tcdAB; EIA Stool sample: tcdA, tcdB, tcdAB: EIA	N/A	sensitivity, specificity, lower limit of detection	In this study, the sensitivities of stool real-time PCR and stool EIA were 95% and 35%, respectively, with a specificity of 100% for both methods. The lower limit of detection of the stool real-time PCR was 30 CFU/ml of stool sample per reaction for tcdA and tcdB. Per the authors, this study highlights the poor performance of stool toxin EIAs in pediatric settings. Direct detection of C. difficile toxin genes in stool samples by real-time PCR showed sensitivity superior to that of stool and culture EIAs and performance comparable to that of real-time PCR assay of cultured isolates.
Noren et al.[21]	2011	Rapid and sensitive loop-mediated isothermal amplification test for Clostridium difficile detection challenges cytotoxin B cell test and culture as gold standard	272 stool specimens	Loop-mediated isothermal amplification (LAMP) test vs. composite cytotoxin B assay (CTBA) and toxigenic culture (TC)	N/A	sensitivity, specificity, positive predictive value, negative predictive value.	This study found that, in using CTBA plus TC as a gold standard for true positive specimens, the LAMP assay displayed a sensitivity and specificity of 98%, and negative (NPV) and positive predictive values (PPV) of 99% and 92%, respectively. The sensitivity and specificity of CTBA alone were 72% and 100%, respectively. An additional four specimens were positive by LAMP test only, but only one of these could be confirmed as a true positive using an in-house PCR detecting C. difficile rpoA. The authors concluded that LAMP proved to be a rapid (1-hour), easily performed, standardized, and accurate test of use for any clinical diagnosing and treating CDI, potentially decreasing morbidity and nosocomial spread of C. difficile.
Pancholi et al.[34]	2012	Detection of toxigenic Clostridium difficile: comparison of the cell culture neutralization, Xpert C. difficile, Xpert C. difficile/Epi, and Illumigene C. difficile assays	200 prospective stool samples and 50 retrospective stool samples	cell cytotoxin neutralization assay (CCNA); the Xpert C. difficile assay; the Xpert C. difficile/Epi assay, and the Illumigene C. difficile assay	N/A	sensitivity, specificity, positive predictive value, negative predictive value.	Of the 200 prospective stool samples tested, 10.5% (n=23) were determined to be positive by CCNA, 17.5% (n=35) were determined to be positive by Illumigene C difficile, and 21.5% (n=43) were determined to be positive by Xpert C. difficile and Xpert C. difficile/Epi in this study. Of the 50 retrospective stools, previously determined to be positive by CCNA, 94% (n=47) were determined to be positive by Illumigene C. difficile and 100% (n=50) were determined to be positive by Xpert C. difficile and Xpert C. difficile/Epi. Of the 11 discrepant results (i.e. negative by illumigene, but positive by both Xpert assays), all were determined to be positive by toxigenic culture. A total of 21% of the isolates presumptively identified by the Xpert C. difficile/Epi as the 027/NAP1/BI strain. The authors concluded that the Xpert C. difficile assays were more sensitive for the detection of toxigenic C. difficile and for the laboratory confirmation of CDI compared to the Illumigene C. difficile assays.

Perry et al.[7]	2010	Evaluation of a chromogenic culture medium for isolation of Clostridium difficile within 24 hours	368 untreated stool samples that were also inoculated onto CLO medium, 339 stool samples that were subject to alcohol shock and inoculated onto 5 distinct selective agars, and standardized suspension of 10 C. difficile ribotypes (untreated and alcohol-treated) that were inoculated onto five distinct selective agars.	prototype chromogenic medium (ID C. difficile prototype [IDCd]) for isolation of C. difficile compared using three different sample groups	N/A	isolate recovery; colony counts	In this study, 236 isolates of C. diff were recovered from 368 untreated stool samples, and all but one of these strains (99.6%) were recovered on IDCd within 24 hours, whereas 74.6% of isolates were recovered on CLO medium after 48 hours. Of 339 alcohol-treated stool samples cultured on IDCd media and five other selective agars, C. diff was recovered from 218 samples using a combination of all media. The authors found that the use of IDCd allowed recovery of 96.3% of isolates within 24 hours, whereas 51 to 83% of isolates were recovered in 24 hours using the five other media. Finally, when they were challenged with pure cultures, all 10 ribotypes of C. diff generated higher colony counts on IDCd irrespective of alcohol pretreatment or duration of incubation.
Ryder et al.[8]	2010	Assessment of Clostridium difficile infections by quantitative detection of tcdB toxin by use of a real-time cell analysis system.	300 consecutively collected stool specimens from patients with suspected C. difficile infection	real-time PCR assay; dual glutamate dehydrogenase and toxin A/B enzyme immunoassay (EIA); and the RTCA assay; compared to a reference standard in combination of the three assays.	N/A	analytical diagnostic sensitivities and specificities of the system for the diagnosis and monitoring of CDI were determined	The authors found that RTCA had a specificity of 99.6% and a sensitivity of 87.5% (28 of 32), which was higher than the EIA result (p=0.005) but lower than the PCR result (P=0.057). The RTCA system detected C. difficile toxins in 29 (9.7%) specimens. Of these, 28 were correctly identified compared to the reference standard. This resulted in sensitivity of 87.5%, a specificity of 99.6%, a positive predictive value (PPV) of 96.5%, and a negative predictive value (NPV) of 98.5%. The sensitivity of the RTCA assay for C. difficile toxin detection was higher than that of the EIA (56.3%; OR=5.44, 95% CI: 1.36-23.54, P=0.0054) but lower than that of PCR (100%; Fisher exact test P=0.057). The positive predictive value (PPV) of the RTCA assay was 96.5%, which was significantly higher than that of the PCR assay (76.2%, OR=8.75, 95% CI 1.03-194.14, Fisher exact P=0.0220). Among the RTCA-positive specimens collected prior to treatment with metronidazole and/or vancomycin, a significant correlation between toxin protein concentrations and clinical CDI severities was observed (R2=0.732, P=0.0004). Toxin concentrations after treatment (0.89 ng/ml) were significantly lower than those prior to the treatment (15.68ng/ml, Wilcoxon P=0.01). The study demonstrates that the RTCA assay provides a functional tool for the potential assessment of C. difficile infections.

Sharp et al.[9]	2010	Evaluation of the C. Diff Quik Chek Complete assay, a new glutamate dehydrogenase and A/B toxin combination lateral flow assay for use in rapid, simple diagnosis of Clostridium difficile disease	284 samples from 261 patients were received for the diagnosis of C. difficile infection and were tested by four assays	GDH antigen-specific EIA [C. Diff Chek-60]; lateral flow assay for toxins A and B [C. Diff Quik Chek]; the C. Diff Quik Chek Complete lateral flow assay [both COMP-GDH and COMP-TOX]; Xpert C. difficile PCR assay	N/A	sensitivities and specificities of these assays	On the basis of these data, the assays tested had the following sensitivities and specificities: GDH-EIA, 100% and 94.2%, respectively; LF-TOX assay, 59.5% and 99.2%, respectively; COMP-GDH assay, 97.6% and 94.6%, respectively; COMP-TOX assay, 61.9% and 99.2%, respectively; and the Xpert C. difficile PCR assay, 100% and 99.6%, respectively. When the C. Diff Quik Check Complete assay was used and two results which were deemed to be indeterminant (GDH-negative and toxin-positive) were discarded, the sensitivity and specificity were 60.0% and 99.6%, respectively. Use of the C. Diff Quik Chek Complete assay with reflex to the Xpert C. difficile PCR assay to test any discrepant samples demonstrated a sensitivity and specificity of 100% and 99.6%, respectively. The authors concluded that use of the combination of the C. Diff Quik Chek Complete assay with reflex to Xpert C. difficile PCR testing for discrepant results provides a rapid, easy, and cost-effective means of accurately diagnosing C. difficile disease.
Shin et al.[38]	2012	Comparison of BD GeneOhm Cdiff and Seegene Seeplex ACE PCR assays using toxigenic Clostridium difficile culture for direct detection of tcdB from stool specimens	243 stool specimens	BD GeneOhm Cdiff assay vs. Seegene Seeplex ACE PCR assay; compared to toxigenic culture.	N/A	sensitivities, specificities, positive predictive values, negative predictive values	The authors of this study determined the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of BD GeneOhm were 95.7% (67/70), 96.5% (167/173), 91.8% (67/73) and 98.2% (167/170), respectively, and those of the Seegene assay were 90.0% (63/70), 97.1% (168/173), 92.6% (38/43), and 96.0% (168/175), respectively. They found no significant differences between BD GeneOhm and Seegene in sensitivity (p=0.325) and specificity (p=0.683). The concordance rate between BD GeneOhm and Seegene was 96.3% (234/243). The authors concluded that both of these commercial PCR assays allow for a rapid and reliable method of detection of tcdB in stool specimen.
Tenover et al.[10]	2010	Impact of strain type on detection of toxigenic Clostridium difficile; comparison of molecular diagnostic and enzyme immunoassay approaches	2,296 eligible unformed stool samples, collected from seven study sites	Xpert C. difficile assay followed by cell culture cytotoxic testing of the isolates and the study sites' standard C. difficile test methods (EIAs).	N/A	sensitivity, specificity, positive predictive value, negative predictive value.	Compared to the results for toxigenic culture with enrichment, the authors of this study found the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the Xpert assay to be 93.5, 94.0, 73.0, and 98.8%, respectively. The overall sensitivity of the EIAs compared to that of enrichment culture was 60.0%, and the sensitivity of the combined GDH algorithms was 72.9%; both were significantly lower than that of Xpert C. difficile (P<0.001 and P=0.03, respectively). They also found that the sensitivity of the EIA was significantly lower than that of the Xpert C. difficile assay for detection of ribotypes 002, 027, and 106 (p<0.0001, p<0.0001, and p=0.004, respectively, Fisher's exact test), and the sensitivity of GDH algorithms for ribotypes other than 027 was lower than that for Xpert C. difficile (P<0.001). The authors concluded that the data suggest that the Xpert C. difficile assay has both the high sensitivity and the high NPV necessary to give clinicians confidence in the laboratory's C. difficile testing results.

Toltzis et al.[39]	2012	High proportion of false-positive Clostridium difficile enzyme immunoassays for toxin A and B in pediatric patients	112 EIA-positive stool samples	EIA-positive stool samples were cultured for toxigenic C. difficile; compared false-positives and true-positives.	N/A	positive predictive value of EIAs	In this study, of the 112 EIA-positive stools cultured, 72 grew toxigenic C. difficile and 40 did not, indicating a positive predictive value of 64% in this population. The estimated prevalence of C. difficile infection (CDI) in the study sites among children tested was 5%-7%. The authors found that children with false-positive EIA results were significantly younger than those with true-positive results but did not differ in other characteristics. They also determined that approximately 1/3 of EIA tests used to evaluate pediatric inpatients for CDI were falsely positive. The authors conclude that the findings from this study suggest that alternative testing strategies should be standard for identifying C. difficile infection in children.
Walkty et al.[49]	2013	Evaluation of an algorithmic approach in comparison with the illumigene assay for laboratory diagnosis of Clostridium difficile infection	428 stool specimens submitted to three clinical microbiology laboratories in Manitoba, Canada, for C. difficile detection	Comparing algorithmic approaches to C. difficile diagnosis with direct testing of stool specimens by a molecular platform (Illumigene C. difficile assay). Algorithm 1: GDH antigen screen followed by toxin A/B antigen testing, with cell cytotoxicity assay for discordant specimens Algorithm 2: GDH antigen screen followed by Illumigene Algorithm 3: GDH antigen screen followed by toxin A/B antigen testing, with Illumigene for discordant specimens	N/A	sensitivity, specificity, positive predictive value	In this study, the prevalence of C. difficile in the stool specimens was 14.7% (63/428) based on toxigenic culture. The sensitivity and specificity of the Illumigene were 73.0% and 99.7%, respectively. The corresponding sensitivities and specificities were 65.1% and 100% for algorithm 1, 68.3% and 100% for algorithm 2, and 69.8% and 100% for algorithm 3. Using algorithm 1, a cell cytotoxicity assay was required for toxin detection in 37% of positive tests, prolonging turnaround time. The authors concluded that the illumigene assay was marginally more sensitive than an algorithmic approach for C. difficile detection in comparison with toxigenic culture as the reference standard. They further concluded that while the sensitivities of both the illumigene assay and the algorithms involving GDH followed by confirmatory or toxin testing were suboptimal, the predictive value of a positive and negative test exceeded 94%, suggesting that either approach may be acceptable for routine use in a clinical microbiology laboratory depending on the prevalence of CDI.

Key question 2: What are effective prevention strategies? (a) What is the effectiveness of current prevention strategies? (b) What are the harms associated with prevention strategies? (c) How sustainable are prevention practices in health care (outpatient, hospital inpatient, extended care) and community settings?							
Havill et al.[30]	2012	Comparison of the microbiological efficacy of hydrogen peroxide vapor and ultraviolet light processes for room decontamination	HPV and UVC processes were performed in 15 patients rooms	Five high-touch sites were sampled before and after the processes and aerobic colony counts (ACCs) were determined	N/A	growth, mean log reduction, statistical significance	In this study, 93% of ACC samples that had growth before HPV did not have growth after HPV, whereas 52% of sites that had growth before UVC did not have growth after UVC (P<0.0001). The mean CD log reduction was >6 for HPV and around 2 for UVC. After HPV, 100% of the 10^4 BIs did not grow, and 22% did not grow after UVC, with a range of 7%-53% for the 5 sites. For the 10^6 BIs, 99% did not grow after HPV and 0% did not grow after UVC. Sites out of direct line of sight were significantly more likely to show growth after UVC than after HPV. Mean cycle time was 153 (range, 140-177) min for HPV and 73 (range, 39-100) min for UVC (P<0.0001). Both HPV and UVC reduce bacterial contaminations, including spores, in patient rooms, but HPV is significantly more effective. UVC is significantly less effective for sites that are out of direct line of sight. The authors concluded that the HPV system was more effective than the UVC system in eliminating aerobic bacteria from surfaces in patient rooms. Unlike HPV, UVC was affected by line of sight. The UVC system was significantly faster and easier to use than the HPV system.
Kassakian et al.[16]	2011	Impact of Chlorhexidine bathing on hospital-acquired infections among general medical patients	Four general medicine units, with a total of 94 beds, at a 719-bed academic tertiary-care facility in Providence, Rhode Island.	7,102 and 7,699 patients were admitted to the medical service in the control and intervention groups, respectively.	N/A	incidence of hospital acquired infections (HAIs)	In this study, the authors found that there was no change in the incidence of C. difficile HAIs (P=0.6)
Kundrapu et al.[31]	2012	Daily disinfection of high-touch surfaces in isolation rooms to reduce contamination of healthcare workers' hands	Of 70 total patients, 34 had CDI	standard cleaning regimen vs. daily cleaning regimen	7 days, or until discharge	percentage of positive cultures; mean number of C. difficile colony forming units (CFU)	For the CDI group in this study, there were no significant differences between the standard cleaning and daily cleaning groups with regard to age (mean, 65 vs. 68 years old, respectively; P=0.53), functional capacity score (2.1 vs. 1.8, respectively; P=0..90), or duration of participation in the study (mean 4.9 vs. 5.2 days, respectively; P=0.59). The authors stated that these findings suggest that daily disinfections of high-touch surfaces in isolation rooms may address an important source of health-care worker hand contamination and provide a useful adjunctive measure to reduce transmission.

Shaughnessy et al.[22]	2011	Evaluation of hospital room assignment and acquisition of Clostridium difficile infection	Among 1844 patients admitted to the ICU, 134 CDI cases were identified. After exclusions, 1,770 patients remained for analysis	room with prior CDI occupant vs. room without prior CDI occupant	N/A	significant association	Of the patients who acquired CDI after admission to the ICU in this study, 4.6% had a prior occupant without CDI, whereas 11.0% had a prior occupant with CDI (P=0.002). The effect of room on CDI acquisition remained a significant risk factor (P=0.008) when Kaplan-Meier curves were used. The prior occupant's CDI status remained significant (P=0.01; hazard ratio, 2.35) when controlling for the current patient's age, acute physiology, and chronic health evaluation III score, exposure to proton pump inhibitors, and antibiotic use. The authors concluded that a prior room occupant with CDI is a significant risk factor for CDI acquisition, independent of established CDI risk factors. They also stated that this finding further highlights the importance of the hospital environment in transmission of serious infections.
Stevens et al.[23]	2011	Cumulative antibiotic exposure over time and the risk of Clostridium difficile infection	The study identified 10,154 hospitalizations for 7,792 unique patients, and 241 cases of CDI, defined as detection of C. difficile toxin in a diarrheal stool sample within 60 days of discharge	retrospective cohort, observed risk of CDI associated with total dose, duration, and number of antibiotics while taking into account the complex changes in exposure over time	N/A	adjusted hazard ratios, significant associations	The authors observed dose-dependent increases in the risk of CDI associated with increasing cumulative dose, number of antibiotics, and days of antibiotic exposure. Compared to patients who received only 1 antibiotic, the adjusted hazard ratios (HRs) for those who received 2, 3 or 4, or 5 or more antibiotics were 2.5 (95% CI: 1.6-4.0), 3.3 (95% CI: 2.2-5.2), and 9.6 (95% CI: 6.1-15.1), respectively. The receipt of fluoroquinolones (as well as cephalosporins, β-lactamase inhibitor combinations, sulfas, and intravenous vancomycin) was associated with an increased risk of CDI, while metronidazole was associated with reduced risk of CDI. The authors concluded that the findings of this study support the overall principles of antimicrobial stewardship.

Key Question 3: What are the comparative effectiveness and harms of antibiotic treatments? (a) Does effectiveness vary by disease severity or strain? (b) Does effectiveness vary by patient characteristics: age, gender, comorbidity, hospital versus community-acquired setting? (c) How do prevention and treatment of CDI affect resistance of other pathogens?							
Cornely et al.[27]	2012	Treatment of first recurrence of Clostridium difficile infection: fidaxomicin versus vancomycin	1164 enrolled in both trials with 178 enrolled for treatment of 1st recurrence: 88 receiving fidaxomicin, 90 receiving vancomycin per-protocol analysis of cure: 79 receiving fidaxomicin, 83 receiving vancomycin 128 patients in the per-protocol analysis of recurrence: 66 treated with fidaxomicin, 62 treated with vancomycin	treatment with fidaxomicin (200 mg twice daily) vs. vancomycin (125 mg 4 times daily)	10 days	primary endpoint: clinical cure of CDI at the end of treatment; secondary endpoint: recurrence within 28 days following clinical cure	In this study, 1164 patients were enrolled, of which a subgroup of 128 in the per-protocol population had another recent episode of CDI prior to the diagnosis at study enrollment. In the analysis of this subgroup, initial response to therapy was similar for both drugs (>90% cure). However, recurrence within 28 days occurred in 35.5% of patients treated with vancomycin and 19.7% of patients treated with fidaxomicin (-15.8% difference, 95% CI: -30.4% to -0.3%l P=0.045). Early recurrence (with 14 days) was reported in 27% of patients treated with vancomycin and 8% of patients treated with fidaxomicin (P=0.003). The authors state that their findings suggest that fidaxomicin or vancomycin treatment of a first recurrence of CDI produces similar initial relief of symptoms (>90% response), but fidaxomicin is superior in preventing a second recurrence within 28 days of completion of therapy. They presumed that preservation of the normal intestinal flora during fidaxomicin treatment is a major factor in the difference in risk of recurrence.
Figueroa et al.[28]	2012	Relapse versus reinfection: recurrent Clostridium difficile infection following treatment with fidaxomicin or vancomycin	90 participants had recurrent CDI and had stool isolates from both initial and recurrent episodes available for typing by REA	Isolates were obtained from 2 randomized, double-blind clinical trials comparing 10 days of treatment with fidaxomicin (200mg twice daily) with treatment with vancomycin (125mg 4 times daily) for CDI.	10 days	Primary endpoint: clinical cure of CDI at the end of 10 days of treatment. CDI recurrence in the 28 (+/- 2)-day follow-up period after the end of therapy was a secondary endpoint.	In this study, patients with isolates available were significantly younger (P=0.008) and more likely to be from Canadian sites (P=0.0001), compared with patients without isolates available. In 75 of 90 subjects (83.3%), the identical REA type strain was identified at recurrence and the initial episode (putative relapse). Early recurrences (0-14 days after treatment completion) were relapses in 86.7% and a new strain (reinfection) in 13.3%. Later recurrences (15-31 days after treatment completion) were relapses in 76.7% and reinfections in 23.3%. Mean time (+/- standard deviation) to recurrence was 12.2 (+/-6.4) days for relapses and 14.7 (+/-6.8) days for reinfections (P=0.177). The most common BI/NAP1/027 group and the previous US epidemic REA group J/NAP2/001 had a significantly higher combined rate of recurrence with the same strain (relapse), compared to the other REA groups (39 of 42 [93%] vs. 36 of 48 [75%], respectively; P=0.023). The authors summarized that their results show a higher than expected rate of recurrent CDI caused by the same isolate as the original episode.

Louie et al.[32]	2012	Fidaxomicin preserves the intestinal microbiome during and after treatment of Clostridium difficile infection (CDI) and reduces both toxin reexpression and recurrence of CDI	Fecal samples were obtained from 89 patients at study entry and on days 4, 10, 14, 21, 28, and 38 for quantitative cultures for C. difficile and cytotoxin B fecal filtrate concentrations.	45 received fidaxomicin, and 44 received vancomycin additionally, samples from 10 patients, each receiving fidaxomicin or vancomycin, and 10 samples from healthy controls were analyzed by quantitative real-time polymerase chain reaction with multiple group-specific primers to evaluate the impact of antibiotic treatment on the microbiome.	N/A	colony forming units (CFU), colony counts, statistical significance	Compared with controls, patients in this study with CDI at study entry had counts of major microbiome components that were 2-3-$\log_{10}$ CFU/g lower. Fidaxomicin allowed major components to persist, whereas vancomycin was associated with a further 2-4-$\log_{10}$ CFU reduction in Bacteroides/Prevotella group organisms, which persisted to day 28 of the study, and shorter term and temporary suppression of both Clostridium coccoides and Clostridium leptum group organisms. In the post treatment period, C. difficile counts similarly persisted in both study populations, but reappearance of toxin in fecal filtrates was observed in 28% of vancomycin-treated patient samples (29 of 94), compared with 14% of fidaxomicin-treated patients (13 of 91; p=0.03) had recurrence of CDI. The authors concluded that whereas vancomycin and fidaxomicin are equally effective in resolving CDI symptoms, preservation of the microflora by fidaxomicin is associated with a lower likelihood of CDI recurrence.
Louie et al.[19]	2011	Fidaxomicin versus vancomycin for Clostridium difficile infection	Adults with acute symptoms of C. difficile infection and a positive result on a stool toxin test were eligible for study entry.	629 patients were randomly assigned to receive fidaxomicin (200mg twice daily) or vancomycin (125mg four times daily) orally for 10 days: 302 received fidaxomicin, and 327 received vancomycin	10 days	primary endpoint: clinical cure secondary endpoint: recurrence of C. difficile infection and global cure	In this study, 548 (87.1%) of patients could be evaluated for the per-protocol analysis. The rates of clinical cure with fidaxomicin were noninferior to those with vancomycin in both the modified intention-to-treat analysis (88.2% with fidaxomicin and 85.8% with vancomycin) and the per-protocol analysis (92.1% and 89.8%, respectively). Significantly fewer patients in the fidaxomicin group than in the vancomycin group had a recurrence of the infection, in both the modified intention-to-treat analysis (15.4% vs. 25.3%, P=0.005) and the per-protocol analysis (13.3% vs. 24.0%, P=0.004). The lower rate of recurrence was seen in the patients with non-North American Pulsed Field type 1 strains. The adverse-event profile was similar for the two therapies. The authors concluded that fidaxomicin and vancomycin have similar effectiveness with respect to the clinical resolution of acute diarrheal disease due to C. difficile infection, but more sustained or durable resolution of disease is achieved with fidaxomicin.

Nerandzic et al.[33]	2012	Reduced acquisition and overgrowth of vancomycin-resistant Enterococci and Candida species in patients treated with fidaxomicin versus vancomycin for Clostridium difficile infection	548 patients (265 treated with fidaxomicin and 283 treated with vancomycin)	141 with both pre-and post-treatment stool specimens for fidaxomicin, and 160 for vancomycin	10 days	VRE and Candida species present before/after treatment; incidence in those who did not have presence prior to treatment. For those with prior VRE, the chance in concentration was compared. The susceptibility of VRE isolates to fidaxomicin was also assessed.	Of 301 patients in this study, 247 (82%) had negative VRE cultures and 252 (84%) had negative candida species cultures before treatment. In comparison with vancomycin-treated patients, fidaxomicin-treated patients had reduced acquisition of VRE (7% vs. 31%, respectively; P<0.001) and Candida species (19 vs. 29%, respectively; P=0.03). For patients with preexisting VRE, the mean concentration decreased significantly in the fidaxomicin group (5.9 vs. 3.8 $\log_{10}$ VRE/g stool; P=0.01) but not the vancomycin group (5.3 vs. 4.2 $\log_{10}$ VRE/g stool; P=0.20). Most VRE isolates recovered after fidaxomicin treatment had elevated fidaxomicin minimum inhibitory concentration (MICs; MIC_{90}, 256µg/ml), and subpopulations of VRE with elevated fidaxomicin MICs were common before therapy. The authors concluded that fidaxomicin was less likely than vancomycin to promote acquisition of VRE and Candida species during CDI treatment.
Pop-Vicas et al.[35]	2012	Empirical antimicrobial prescriptions in patients with Clostridium difficile infection at hospital admission and impact on clinical outcome	94 patients with CDI at hospital admission	Non-CDI-related antimicrobials	Not stated	Odds ratios for non-CDI-related antimicrobial use, duration, and adverse clinical outcomes	Among the 94 patients in this study with CDI at hospital admission, 62% received at least one non-CDI-related antimicrobial during their hospitalization for CDI. Severe complicated CDI (OR: 7.1, 95% CI: 1.8-28.5, P=0.005), duration of non-CDI-related antimicrobial exposure (OR: 1.2, 95% CI: 1.03-1.36); P=0.16), and age (OR: 1.1, 95% CI: 1.0-1.1, P=0.043) were independent risk factors for adverse clinical outcomes. 1/3 of the patients received unnecessary antimicrobial therapy. Sepsis at hospital admission (OR: 5.3, 95% CI: 1.8-15.8, P=0.003) and clinical suspicion of urinary tract infection (OR: 9.7, 95% CI: 2.9-32.3, P<0.001) were independently associated with unnecessary antimicrobial prescriptions. The authors found that empirical use of non-CDI-related antimicrobials was common, and that prolonged exposure to non-CDI-related antimicrobials was associated with adverse clinical outcomes, including increased in-hospital mortality.
Sears et al.[37]	2012	Fidaxomicin attains high fecal concentrations with minimal plasma concentrations following oral administration in patients with Clostridium difficile infection	1147 patients received ≥1 dose of treatment	Fidaxomicin 200 mg every 12 hours (564 patients) vs. vancomycin 125 mg every 6 hours	10 days	plasma and stool concentrations of fidaxomicin and vancomycin	In this study population, plasma concentrations were low for both fidaxomicin (mean +/- standard deviation, 22.8 +/-26.7 ng/mL and 28.5 +/- 33.4 ng/mL on the first and last days of therapy, respectively) and OP-1118 (mean +/- standard deviation, 44.5 +/- 50.4 ng/mL and 85.6 +/- 131 ng/mL, respectively). In contrast, fecal levels were >1000 µg/g for fidaxomicin and >800 µg/g for OP-1118. Fidaxomicin mean fecal levels were >5000 times the minimum inhibitory concentration for C. difficile of 0.25 µg/mL. The authors found that fidaxomicin achieves fecal concentrations that are well within excess of the MIC_{90} for C. difficile and is consistent with a high level of activity toward the target organism at the intended site of action in the colon.

Shaughnessy et al.[47]	2013	Unnecessary antimicrobial use in patients with current or recent Clostridium difficile infection	patients with new-onset CDI diagnosed at the MVAMC without another diagnosis of CDI in the prior 30 days	observational: two infectious disease physicians independently assessed non-CDI antimicrobial use	N/A	risk factors associated with unnecessary antimicrobial use	Of the 246 patients that were reviewed with new onset CDI, 141 (57%) received non-CDI antimicrobials during and/or after their CDI treatment, totaling 2,147 antimicrobial days and 445 antimicrobial courses. The two reviewers agreed on the necessity of antimicrobials in more than 99% cases. (85% initially, 14% after discussion). 77% of patients received at least 1 unnecessary antimicrobial dose, 26% of patients received only unnecessary antimicrobials, and 45% of total non-CDI antimicrobial days included unnecessary antimicrobials. The primary reasons for unnecessary antimicrobials were putative urinary tract infection and pneumonia. Drug classes frequently used unnecessarily were fluoroquinolones and β-lactams. In conclusion, at the authors' institution, non-CDI antimicrobials are often used unnecessarily in patients with current or a recent history of CDI.
Sydnor et al.[24]	2011	Antimicrobial prescribing practices in response to different Clostridium difficile diagnostic methodologies	adult inpatients at Johns Hopkins Hospital with positive GDH stool testing for CDI during two periods between January and August 2009. 200 patients enrolled; 100 in each time period	observational; whether or not the patients were prescribed empiric anti-CDI therapy	N/A	compared mean duration of empiric anti-CDI therapy between those with negative confirmatory testing during the two time periods	Of patients who ruled out for CDI in this study, those with confirmatory testing by PCR received an average of 11.4 hours of anti-CDI therapy as compared with 47.1 hours for those who underwent confirmatory testing by CCCNA (P=0.02). 94 (49%) of 191 patients had confirmed CDI by either CCCNA or PCR testing. 5 (3%) were found to have asymptomatic carriage of C. difficile, and all were inappropriately treated with antimicrobials. The authors summarized their findings by suggesting a 2-step testing algorithm for C. difficile using rapid PCR confirmatory testing rather than CCCNA leads to decreased unnecessary anti-CDI antimicrobial use.
Weiss et al.[40]	2012	Safety analysis of Fidaxomicin in comparison with oral vancomycin for Clostridium difficile infections	A total of 728 adults have received oral fidaxomicin in clinical trials to date	116 healthy volunteers and 612 patients with C. difficile infection	N/A; various trials	tolerability, safety profile (compared to vancomycin)	In this safety analysis of phase 3 clinical trials, fidaxomicin was well-tolerated, with a safety profile comparable with oral vancomycin. The authors found were no differences in the incidence of death or serious adverse events between the 2 drugs. They concluded that fidaxomicin appeared to be well-tolerated, but that continued monitoring of adverse events is necessary.
Key Question 4: What are the effectiveness and harms of nonstandard adjunctive interventions? (a) In patients with relapse/recurrent CDI?							
Aldeyab et al.[11]	2011	An evaluation of the impact of single-dose intravenous immunoglobulin regimen in the treatment of Clostridium difficile infections	Case-control design: Cases involved patients who received a combination of the standard treatment (i.e. metronidazole and/or vancomycin) and intravenous immunoglobulin treatment, and controls were patients who received only the standard treatment.	metronidazole and/or vancomycin (standard treatment) plus intravenous immunoglobulin treatment (400 mg/kg given in severe cases or in the event of no clinical response to standard treatment) vs. standard treatment	N/A; single dose of experimental treatment	Means for differences between case patients and controls in relation to total length of hospital stay were compared	In this study population, a total of 78% of case patients and 83% of controls were treated with probiotics. For 17% of case patients and controls, illness was severe at the date of positive toxin test result. The median length of stay in the hospital until discharge following the first positive CDI toxin test was 36 days for the case patients compared with 33 days for controls (difference not statistically significant, p=.779). No statistically significant differences were observed in relation to the other studied outcomes. The authors stated that results of this research highlight the need for further investigations aimed at measuring serum antibody levels to C. difficile toxin A and then defining an effective intravenous immunoglobulin therapy course for the management of CDL.

Allen et al.[41]	2013	Lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhoea and Clostridium difficile diarrhoea in older inpatients (PLACIDE): a randomised, double-blind, placebo-controlled, multicentre trial	Inpatients aged 65 years and older and exposed to one or more oral or parenteral antibiotics.	multistrain preparation of lactobacilli and bifidobacteria once per day (1470 patients) vs. and identical placebo (1471 patients)	21 days	Occurrence of AAD within 8 weeks and C. difficile diarrhea (CDD) within 12 weeks of recruitment	AAD (including CDD) occurred in 159 (10.8%) participants in the microbial preparation group and 153 (10.4%) participants in the placebo group (relative risk [RR]: 1.04; 95% CI: 0.84-1.28; P=0.71). CDD was an uncommon cause of AAD and occurred in 12 (0.8%) participants in the microbial preparation group and 17 (1.2%) participants in the placebo group (RR: 0.71; 95% CI: 0.34-1.47; P=0.35). 578 (19.7%) participants had one or more serious adverse event; the frequency of serious adverse events was much the same in the two study groups and none was attributed to participation in the trial. The authors identified no evidence that a multistrain preparation of lactobacilli and bifidobacteria was effective in prevention of AAD or CDD. An improved understanding of the pathophysiology of AAD is needed to guide future studies.
Gao et al.[5]	2010	Dose-response efficacy of a proprietary probiotic formula of Lactobacillus acidophilus CL1285 and Lactobacillus casei LBC80R for antibiotic-associated diarrhea and Clostridium difficile-associated diarrhea prophylaxis in adult patients	255 adult inpatients	patients were randomized into three groups: i: two probiotic capsules per day (n=86) [Pro-2] ii: one probiotic capsule and one placebo per day (n=85) [Pro-1] iii: two placebo capsules per day (n=84) [placebo]	prophylaxis began within 36 hours of initial antibiotic treatment, continued for 5 days after last antibiotic treatment, and patients were followed for 21 additional days	Incidence of AAD, symptom duration, CDAD incidence, frequency of GI symptoms	The Pro-2 arm of this study (15.5%) had a lower AAD incidence vs. Pro-1 (28.2%). Each probiotic group had a lower AAD incidence vs. placebo (44.1%). In patients who acquired AAD, Pro-2 (2.8 days) and Pro-1 (4.1 days) had shorter symptom duration vs. placebo (6.4 days). Similarly, Pro-2 (1.2%) had a lower CDAD incidence vs. Pro-1 (9.4%). Each treatment group had a lower incidence vs. placebo (23.8%). Gastrointestinal symptoms were less common in the treatment groups vs. placebo and in Pro-2 vs. Pro-1. Overall, the authors believed this study represents the highest quality trial of probiotic prophylaxis for AAD and CDAD in adults. The proprietary probiotic blend used in this study was well-tolerated and effective for reducing risk of AAD and, in particular, CDAD in hospitalized patients on antibiotics. The authors also noted a dose-ranging effect was shown with 100 billion CFU, yielding superior outcomes and fewer gastrointestinal events compared to 50 billion CFU.

Pozzoni et al.[36]	2012	Saccharomyces boulardii for the prevention of antibiotic-associated diarrhea in adult hospitalized patients: a single-center, randomized, double-blind, placebo-controlled trial.	Patients being prescribed antibiotics or on antibiotic therapy for <48 hours were eligible	Of 562 consecutive eligible patients, 275 patients aged 79.2 +/- 9.8 years (134 on placebo) were randomized and 204 aged 78.4 +/- 10 years (98 on placebo) completed the follow-up	Started treatment (or placebo) within 48h of beginning antibiotic therapy, continued treatment for 7 days, and were followed for 12 weeks after ending antibiotic treatment	development of antibiotic-associated diarrhea (AAD); odds ratios; mortality rates	In this study population AAD developed in 13.3% (13/98) of the patients receiving placebo and in 15.1% (16/106) of those receiving S. boulardii (OR for S. boulardii vs. placebo, 1.16; 95% CI 0.53-2.56). Five cases of CDAD occurred, two in the placebo group (2.0%) and 3 in the probiotic group (2.8%; OR for S. boulardii vs. placebo, 1.40; 95% CI 0.23-8.55). There was no difference in mortality rates (12.7% vs. 15.6%, P=0.60). The authors reported a total of 94 adverse events that were reported (52 in the S. boulardii group and 42 in the placebo group, P=0.37) in 41 patients who were assigned to received S. boulardii and 35 who were assigned to receive placebo. Adverse events included constipation, abdominal pain, pruritus, headache, cutaneous rash, and fever unrelated to underlying infection. All adverse events were mild with no cases of fungemia. The authors concluded that S. boulardii was unable to prevent the development of AAD, at least in a context with a low incidence of AAD cases.
van Nood et al.[48]	2013	Duodenal infusion of donor feces for recurrent Clostridium difficile	43 patients randomly assigned to three different treatment arms; 41 completed study protocol	i: donor feces infusion (n=16) ii: vancomycin only (n=13) iii: vancomycin and bowel lavage (n=13)	Planned 10 weeks; however study was terminated after an interim analysis	resolution of diarrhea associated with C. difficile infection without relapse after 10 weeks	Of the 16 patients in the infusion group in this study, 13 (81%) had resolution of C. difficile-associated diarrhea after the first infusion. The remaining three patients received a second infusion with feces from a different donor, with resolution in two patients. Resolution of C. difficile infection occurred in 4 of 13 patients (31%) receiving vancomycin alone and in 3 of 13 patients (23%) receiving vancomycin with bowel lavage (P<0.001 for both comparisons with the infusion group). No significant differences in adverse events among the three study groups were observed except for mild diarrhea and abdominal cramping in the infusion group on the infusion day. After donor-feces infusion, patients showed increased fecal bacterial diversity, similar to that in healthy donors, with an increase in Bacteroides species and clostridium clusters IV and XIVa and a decrease in Proteobacteria species. The authors concluded that infusion of donor feces was significantly more effective for the treatment of recurrent C. difficile infection than the use of vancomycin. In particular, patients with multiple relapses of C. difficile infection benefited from this new approach.

Appendix C: Evidence Table (Cycle 1/1st Assessment)

Author	Year	Trial	n	Subjects	Primary Outcome	Duration	Findings
Key Question 1: How do different methods for detection of toxigenic *C. difficile* to assist with diagnosis of CDI compare in their sensitivity and specificity? (a) Do the differences in performance measures vary with sample characteristics?							
Dubberke[4]	2011	Not applicable	n = 150	-Median age = 60 yrs -50.7% Female -70.0% White	Sensitivity, specificity and predictive values of assays to diagnose CDI with and without including patient characteristics compared with reference of stool culture.	Specimens collected over 6 month period	Minimal changes in sensitivity, but lower specificity for assays Tox A/B II, C. diff Chek-60, BD GeneOhm Cdiff, Xpert C. difficile, and Illumigene C. difficile; p<0.01
Deshpande [5]	2011	Meta-analysis	19 studies; 7392 samples	Not reported	Sensitivity and specificity of CDI	Not reported	Real-time PCR has 90% sensitivity and 96% specificity for diagnosing CDI compared with cell culture cytotoxicity neutralization assays or anaerobic toxigenic culture.
Key Question 2. What are effective prevention strategies? (a) What is the effectiveness of current prevention strategies? (b) What are the harms associated with prevention strategies? 3 (c) How sustainable are prevention practices in health care (outpatient, hospital inpatient, extended care) and community settings?							
Bearman[6]	2010	Prospective before-after	Standard precautions: 3486 patient days Universal gloving: 4392 patient days	Surgical ICU academic medical center	Compliance rates, device-related infection, CDI	Standard precautions: 3486 patient days Universal gloving: 4392 patient days	No difference between standard precautions and universal gloving with emollient-impregnated gloves (p = 0.53)
Kassakian[7]	2011	Quasi-experimental	Control: n = 7102 Intervention n = 7699	-Patients at an academic hospital in a general medical ward -Mean age control: 61.5 yrs; intervention: 60.7 yrs	Composite incidence of MRSA and VRE hospital acquired infections	Patient-days control: 34,800; intervention: 36,185	No change in the incidence of *C. difficile* hospital acquired infections (p = 0.6)
Key Question 3: What are the comparative effectiveness and harms of different antibiotic treatments? (a) Does effectiveness vary by disease severity or strain? (b) Does effectiveness vary by patient characteristics: age, gender, comorbidity, hospital versus community-acquired setting? (c) How do prevention and treatment of CDI affect resistance of other pathogens?							
Crook[8]	**2012**	Meta-analysis of 2 phase three RCCT	n = 1164	-Fiadxomicin 200 mg twice daily for 10 days -Vancomycin 125 mg four times daily for 10 days	Persistent diarrhea, recurrence of CDI, or death	36-40 days after randomization.	Compared with vancomycin, fidaxomicin reduced persistent diarrhea, CDI recurrence, and death by 40% (p<0.001)
Mullane[9]	**2011**	Meta-analysis of 2 phase three RCCT	n = 192 -Fidaxomicin = 90 - Vancomycin = 102	-Fiadxomicin 200 mg twice daily for 10 days -Vancomycin 125 mg four times daily for 10 days	Recurrence, clinical cure	36-40 days after randomization	Cure rate 90% for fidaxomicin a,d 79.4% for vancomycin (p = 0.04); Fidaxomicin had 12.3 fewer recurrences compared with vancomycin (p = 0.48).

Key Question 4: What are the effectiveness and harms of nonstandard adjunctive interventions? (a) In patients with relapse/recurrent CDI?							
Gough[10]	**2011**	Case series	Patients = 317 Case series and reports = 27	-Average age = 53 yrs -61% Female	Disease resolution	Range: 36 hours-5 yrs	92% of patients experienced resolution

Appendix D

Surveillance and Identification of Triggers for Updating Systematic Reviews for the EHC Program

Title: **Effectiveness of Early Diagnosis, Prevention, and Treatment of *Clostridium difficile* Infection**

Name of Person Completing the Form: _____

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Key Question 1: How do Different Methods for Detection of Toxigenic C. difficile Compare in Their Sensitivity and Specificity?			
Immunoassays for toxins A and B Ten studies directly compared at least 2 immunoassays for toxins A and B, providing 16 pairwise comparisons of 7 different immunoassays. Comparative data were not found for many currently used tests. There were no statistical differences between the sensitivities of immunoassays that were compared; however, the estimates of the differences in sensitivity were not very precise and could not rule out substantial differences. Substantial differences in false positives, that is, specificity, were not found among the tests that were compared. (Low to moderate)	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Gene detection tests versus immunoassays for toxins A and B Four studies compared at least one toxin gene detection test to at least one immunoassay for toxins A and B, providing a total of nine direct comparisons. Comparative data were not always available for the three currently available gene detection tests. The gene detection tests could be substantially more sensitive than many immunoassays for toxins A and B, with no or relatively modest loss of specificity. (Low to moderate)	☐	New Evidence:	☐
Patient characteristics Insufficient patient information was provided in reports of comparative data. (Insufficient)	☐	New Evidence:	☐
Key Question 2: What are Effective Prevention Strategies?			
Antibiotic use Sixteen studies, including six bundled prevention practice studies, found appropriate prescribing practices are associated with decreased CDI incidence. Harms were not reported. (Low)	☐	New Evidence:	☐
Gloves One controlled trial found use of gloves in hospital settings reduced CDI incidence. (Low)	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Disposable thermometer Three time series/before–after studies, two with controls, found use of disposable thermometers in hospital settings reduced CDI incidence. (Low)	☐	New Evidence:	☐
Handwashing/alcohol gel No study examined whether handwashing reduced CDI incidence. Two studies, one controlled trial and one before–after study, of use of alcohol gel to reduce MRSA transmission did not find significant differences in CDI incidence. (Low)	☐	New Evidence:	☐
Disinfection Thirteen before–after studies of outbreaks or endemic hospital settings found intensive disinfection with a chemical compound that kills C. difficile spores reduced CDI incidence. (Low)	☐	New Evidence:	☐
Sustainability No evidence was available. (Insufficient)	☐	New Evidence:	☐
Risk factors Ten observational studies found evidence that antibiotic use, whether specific or general, increased risk of CDI. Severe underlying disease, acid suppression, and age are indicated as risk factors. A number of other potential factors may be indicated in single studies. (Low)	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Multiple component strategies Eleven time series/before–after studies examined bundles of prevention components in a single intervention. Data are insufficient to draw conclusions. Harms were not reported. (Insufficient)	☐	New Evidence:	☐
Key Question 3: What are the Comparative Effectiveness and Harms of Different Antibiotic Treatments?			
Vancomycin versus metronidazole There were 3 head-to-head trials with a total of 335 subjects. Trials used various definitions of CDI patient and cure, especially with regard to stool count and consistency. No significant differences in outcomes, including initial cure, clinical recurrence, and mean days to resolved diarrhea, were found. Our results build upon, and are consistent with, the Cochrane Reviews search completed by Bricker et al. (Moderate for clinical cure, low for all other outcomes)	☐	New Evidence:	☐
Severe disease, vancomycin versus metronidazole One RCT examined a prespecified subgroup of 69 subjects with severe CDI; improved clinical cure was based on per-protocol analysis, but not with strict intention-to-treat analysis. (Insufficient)	☐	New Evidence:	☐
Fidaxomicin versus vancomycin One large, high-quality RCT demonstrated decreased recurrence among those receiving fidaxomicin. (Moderate)	☐	New Evidence:	☐
All other comparisons of standard treatments There were eight trials examining: vancomycin versus bacitracin (two trials), vancomycin versus fidaxomicin,	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
vancomycin versus nitazoxanide, vancomycin high versus low dose, vancomycin versus placebo, metronidazole versus nitazoxanide, and metronidazole versus metronidazole plus rifampin (one each). No differences. (Moderate for vancomycin versus fidaxomicin, low for all other comparisons)			
Strain of organism One RCT (fidaxomicin vs. vancomycin) demonstrated decreased recurrence among those receiving fidaxomicin when the infecting organism was a non-NAP1 strain. (Low)	☐	New Evidence:	☐
Patient characteristics No comparative data were available. (Insufficient)	☐	New Evidence:	☐
Resistance of other pathogens No data were available. (Insufficient)	☐	New Evidence:	☐
Key Question 4: What are the Effectiveness and Harms of Nonstandard Adjunctive Interventions?			
Treating CDI, active control Probiotics, prebiotics, C. difficile immune whey, and colestipol are not more effective in treating CDI than standard antibiotic treatment with oral vancomycin or metronidazole or placebo. (Low)	☐	New Evidence:	☐
Treating CDI, placebo Administration of a probiotic with live bacteria to treat CDI in critically ill patients increases risk for greater morbidity and mortality from fungemia without any known benefit. (Low)	☐	New Evidence:	☐
Treating recurrent CDI There is limited evidence from two case series that	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
fecal flora reconstitution is effective in treating recurrent CDI for up to 1 year. (Low)			
Preventing CDI There is limited evidence that the nonstandard interventions in this review are not more effective than placebo for primary prevention of CDI. (Low)	☐	New Evidence:	☐
Preventing recurrent CDI There is limited evidence from one subgroup analysis that a prebiotic may reduce diarrhea recurrence in patients treated for CDI more so than placebo with standard antibiotics. There is limited moderate-strength evidence from one study that monoclonal antibodies are effective in preventing recurrence of CDI. (Low to moderate)	☐	New Evidence:	☐
Are there new data that could inform the key questions that might not be addressed in the conclusions?			